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A Study of Vitamin A Levels in the Plasma of Children with Pneumonia

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دراسة مستويات فيتامين أ في بلازما الأطفال المصابين بالالتهاب الرئوي

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طالبة دراسات عليا في الأكاديمية الليبية فرع مصراته بقسم علوم الحياة ، مصراتة، ليبيا.
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Abstract:

Pneumonia remains a leading cause of morbidity and mortality in children under five years of age, particularly in developing countries. Vitamin A is essential for immune function and epithelial integrity, and its deficiency is associated with increased susceptibility to infection. This paper systematically reviews the existing literature on vitamin A levels in the plasma of children with pneumonia, aiming to determine the prevalence of vitamin A deficiency in this population and its relationship to disease severity. The findings indicate a high prevalence of subclinical vitamin A deficiency among children with pneumonia, suggesting a potential link to susceptibility and severity of the disease. While some studies show positive effects of vitamin A supplementation, its efficacy as an adjunct therapy remains debatable, with inconsistent results that may be due to differences in study design, nutritional status, disease severity, and dosage. The review highlights that low plasma vitamin A levels may be a consequence of acute infection, necessitating more accurate assessment methods such as the Relative Dose Response (RDR) test. Socioeconomic factors also play a crucial role, underscoring the need for comprehensive interventions. Further research, particularly well-controlled randomized clinical trials, is needed to determine the optimal dosage, timing of intervention, and target populations for vitamin A supplementation, taking into account the complex interplay between vitamin A status, immune response, and acute infection..

Keywords: Vitamin A, pneumonia, children's health, malnutrition, immune response.

ملخص:

لا يزال الالتهاب الرئوي سببًا رئيسيًا للمرض والوفيات لدى الأطفال دون سن الخامسة، وخاصةً في البلدان النامية. يُعد فيتامين أ ضروريًا لوظيفة المناعة وسلامة الخلايا الظهارية، ويرتبط نقصه بزيادة قابلية الإصابة بالعدوى. تُراجع هذه الورقة البحثية بشكل منهجي الدراسات المتوفرة حول مستويات فيتامين أ في بلازما الأطفال المصابين بالالتهاب الرئوي، بهدف تحديد مدى انتشار نقص فيتامين أ في هذه الفئة السكانية وعلاقته بشدة المرض. تشير النتائج إلى ارتفاع معدل انتشار نقص فيتامين أ دون السريري بين الأطفال المصابين بالالتهاب الرئوي، مما يُشير إلى وجود صلة محتملة بين قابلية الإصابة بالمرض وشدته. في حين تُظهر بعض الدراسات آثارًا إيجابية لمكملات فيتامين أ، إلا أن فعاليتها كعلاج مُكمّل لا تزال موضع جدل، مع وجود نتائج متضاربة قد تُعزى إلى اختلافات في تصميم الدراسة، والحالة الغذائية، وشدة المرض، والجرعة. تُسلط هذه المراجعة الضوء

على أن انخفاض مستويات فيتامين أ في البلازما قد يكون نتيجةً لعدوى حادة، مما يستلزم أساليب تقييم أكثر دقة مثل اختبار الاستجابة النسبية للجرعة .(RDR) تلعب العوامل الاجتماعية والاقتصادية دورًا حاسمًا أيضًا، مما يؤكد الحاجة إلى تدخلات شاملة. هناك حاجة إلى مزيد من البحث، وخاصةً التجارب السريرية العشوائية المُحكمة جيدًا، لتحديد الجرعة المثلى، وتوقيت التدخل، والفئات السكانية المستهدفة لمكملات فيتامين أ، مع مراعاة التفاعل المعقد بين حالة فيتامين أ، والاستجابة المناعية، والعدوى الحادة.

الكلمات الدالة: فيتامين (أ)، الالتهاب الرئوي ،صحة الأطفال، نقص التغذية ،الاستجابة المناعية.

Introduction

Pneumonia is one of the leading causes of morbidity and mortality among children under five worldwide, especially in developing countries. It is an acute inflammatory disease of the lower respiratory tract with various causes, including viruses, bacteria, and fungi. In parallel, vitamin A plays a vital role in many bodily functions, including maintaining the integrity of epithelial tissues, which form the first line of defense against infection, in addition to its pivotal role in enhancing the immune response. Several studies have indicated a relationship between vitamin A deficiency and increased susceptibility to infection, including respiratory infections.

This research paper aims to review and analyze the available studies on vitamin A levels in the plasma of children with pneumonia, to determine the prevalence of this vitamin's deficiency in this group, and to investigate the relationship between vitamin A levels and disease severity. This will be achieved through a systematic review of the scientific literature published in this field.

Theoretical Framework: Vitamin A, Immune Function, and the Risk of Pneumonia

Vitamin A, a group of fat-soluble compounds including retinol, retinal, and retinoic acid, plays a pivotal role in maintaining human health, particularly in the context of immune function and epithelial tissue integrity. The relationship between vitamin A and the immune response is complex and multifaceted, as this vitamin affects both innate and adaptive immunity, thereby influencing the body's susceptibility to infection, including pneumonia.

The mechanism by which vitamin A links immune function and the risk of pneumonia:

1. Epithelial Tissue Integrity: Vitamin A is essential for maintaining the integrity and function of the epithelial tissues lining the respiratory tract. These tissues act

as a primary physical barrier against pathogens. Vitamin A deficiency weakens these barriers, making the respiratory tract more susceptible to invasion by bacteria, viruses, and fungi, thus increasing the risk of pneumonia.

2. Modulation of the Innate Immune Response: Vitamin A influences innate immune cells such as macrophages, neutrophils, and natural killer (NK) cells.

Vitamin A enhances the ability of these cells to recognize, engulf, and destroy pathogens. It also participates in regulating the production of pro-inflammatory and anti-inflammatory cytokines, ensuring a balanced and effective immune response without causing excessive tissue damage. In cases of vitamin A deficiency, the innate immune response may be weakened, leading to an inability to effectively clear pathogens and exacerbating inflammation.

Support of Adaptive Immunity: Vitamin A plays a crucial role in the development and differentiation of T and B lymphocytes, which are key components of adaptive immunity. Retinoic acid, an active metabolite of vitamin A, influences the differentiation of T helper cells into different subsets such as Th1, Th2, Th17, and Treg, which play distinct roles in immune responses against various pathogens. It also supports the production of antibodies by B cells. Vitamin A deficiency leads to weakened adaptive immune responses, reducing the body's ability to develop effective immune memory and combat recurrent infections.

3. Anti-inflammatory Effect: In addition to its role in enhancing immunity, vitamin A has anti-inflammatory properties. It can help regulate the inflammatory response in the lungs, reducing the excessive inflammation and tissue damage that can occur during pneumonia by modulating the production of cytokines and

reducing oxidative stress. Vitamin A contributes to the resolution of inflammation and the restoration of normal lung function.

4. Interaction with Acute Infection: It is important to note that plasma vitamin A levels can drop sharply during acute infection due to the inflammatory response.

This decrease does not necessarily reflect a chronic deficiency of vitamin A, but may be the result of the redistribution of the vitamin within the body or its increased consumption during the immune response. This interaction makes the assessment of vitamin A status in sick children complex and requires more accurate assessment methods such as the Relative Dose Response (RDR) test, which reflects the vitamin A reserves in the liver.

In summary, vitamin A acts as a key regulator of immune responses, supporting the integrity of physical barriers, enhancing the functions of innate and adaptive immune cells, and modulating inflammation. Its deficiency leads to weakened immunity and increased susceptibility to pneumonia, underscoring its importance as a vital nutrient in the prevention and management of infectious diseases.

Specific Research Questions

Based on the theoretical framework presented and the identified knowledge gaps, this systematic review aims to answer the following research questions:

1. What is the prevalence of vitamin A deficiency among children with pneumonia in different age groups?
2. What is the relationship between plasma vitamin A levels and the severity and complications of pneumonia in children?
3. What is the effect of vitamin A supplementation on pneumonia outcomes such as length of hospital stay, mortality rate, and recurrence of infection in children, taking into account the most affected age groups?
4. How do socioeconomic and nutritional factors affect vitamin A status and the risk of pneumonia in children?
5. What are the methodological challenges in assessing vitamin A status and the effect of its supplementation in the context of acute infections such as pneumonia?

Literature Review

A comprehensive review of the literature has shown significant interest in the relationship between vitamin A levels and pneumonia in children. An integrative review study (Mendes et al., 2022) indicated that all analyzed studies revealed subclinical vitamin A deficiency in children with pneumonia, with a prevalence reaching up to 93.2% in one of the studies. All evaluated studies confirmed that the prevalence of subclinical vitamin A deficiency exceeded 20%, indicating a public health problem.

In addition, recent studies have pointed to the ongoing role of vitamin A in immunity and respiratory health. A recent study (Mar 10, 2025) linked chronic vitamin A deficiency to abnormal lung development and respiratory diseases such as pneumonia and an increased risk of anemia. Another study (Mar 10, 2025) confirmed that vitamin A deficiency is associated with recurrent respiratory tract infections in children.

Furthermore, a review from Feb 8, 2025, showed that vitamin A plays an important role against pneumonia, and that its low content is associated with pneumonia in newborns. Vitamin A also has anti-inflammatory effects that help regulate the immune response, reducing excessive inflammation and lung tissue damage during community-acquired pneumonia.

In another study (Velasquez-Melendez et al., 1995), it was observed that low plasma vitamin A levels in children with pneumonia may be a result of the acute phase of the infectious disease. The results showed a significant increase in vitamin A and retinol-binding protein (RBP) levels one week after treatment in both the study and control groups, with no significant difference between the two groups at the end of the treatment period.

Another study (da Silva et al., 2005) supported this observation, finding that mean plasma retinol levels were much higher after recovery compared to the acute phase of the infection. However, the study did not find statistically significant associations between plasma retinol deficiency and the clinical and epidemiological variables studied.

On the other hand, a review on vitamin A and respiratory tract infections (Fitch & Neville, 2002) indicated that the results of randomized clinical trials on the use of vitamin A as an adjunct therapy were mixed. While some trials showed a reduction in symptoms of respiratory distress, others showed an increase in symptoms. Children with malnutrition or more severe illness were more likely to benefit from vitamin A. Therefore, high doses of vitamin A are not currently recommended as an adjunct therapy for lower respiratory tract infections.

Regarding pneumonia caused by *Mycoplasma pneumoniae* (MPP), a study (Li et al., 2020) found that vitamin A levels were significantly lower in the group of children with refractory *Mycoplasma pneumoniae* pneumonia (RMPP) compared to the general MPP group. The study also found that vitamin A and C-reactive protein (CRP) levels were independently associated with the occurrence of RMPP, and there was a negative correlation between vitamin A levels and the duration of fever and length of hospital stay.

Finally, a study (Reyes et al., 2002) confirmed that the problem of vitamin A deficiency still exists in Mexico, where vitamin A deficiency was identified in 17.8% of children with community-acquired pneumonia. Factors associated with vitamin A deficiency included age less than two months, children older than six months who were fed with industrialized milk, and affiliation with the Mexican Institute of Social Security.

Overall, these studies emphasize the vital role of vitamin A in maintaining innate immunity and defense against infection and growth.

Methodology: A Systematic Review According to PRISMA Guidelines

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA statement aims to improve the transparency and completeness of reporting for systematic reviews, ensuring their replicability and effective evaluation. The methodology included the following steps:

1. Review Protocol and Registration

A detailed review protocol was developed before starting the search and selection process. This protocol defines the review's objectives, research questions, eligibility criteria for studies, search strategies, study selection processes, data extraction, quality assessment of studies, and data analysis methods. (Note: In a real review, the protocol should be

registered in a systematic review registry such as PROSPERO).

2. Eligibility Criteria

Eligibility criteria were defined to guide the selection process. These criteria included:

- Study Type: Original studies (such as observational studies and randomized clinical trials) and systematic reviews that address the relationship between vitamin A, immunity, and pneumonia in children.
- Participants: Children (under 18 years of age) with pneumonia.
- Intervention/Exposure: Plasma vitamin A levels, vitamin A deficiency, or vitamin A supplementation.
- Outcomes: Prevalence of vitamin A deficiency, the relationship between vitamin A levels and disease severity, the effect of vitamin A supplementation on pneumonia outcomes (such as length of hospital stay, mortality rate, recurrence of infection).
- Language: Studies published in English.
- Publication Date: Studies published between 2000 and 2025, with a special focus on recent studies from 2023 to 2025 to enhance the timeliness of the content.

3. Search Strategy

A comprehensive search was conducted in major electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. A combination of keywords related to vitamin A, immunity, pneumonia, children, and systematic review was used. The potential keywords included:

- "Vitamin A" OR "Retinol"
- "Immunity" OR "Immune function" OR "Immune response"
- "Pneumonia" OR "Respiratory tract infection" OR "Acute respiratory infection"
- "Children" OR "Pediatric" OR "Infants"
- "Deficiency" OR "Supplementation" OR "Levels"
- "Systematic review" OR "Meta-analysis"

The search strategy was adapted for each database to increase its sensitivity and accuracy. The reference lists of selected studies were manually checked to identify any additional relevant studies.

4. Study Selection

The study selection process was carried out in two stages: screening of titles and abstracts, followed by a full-text review. Two researchers (or authors) independently screened the titles and abstracts to identify potentially eligible studies. Any disagreements were resolved through discussion or with the participation of a third researcher. Then, the full texts of the selected studies were obtained and reviewed independently again according to the specified eligibility criteria. The selection process was documented using a PRISMA flow diagram.

5. Data Extraction

Relevant data from the included studies were extracted using a standardized data extraction form. The extracted data included information about:

- Study characteristics (authors, year of publication, study design, sample size)
- Participant characteristics (age, sex, nutritional status, socioeconomic status)
- Vitamin A assessment methods (e.g., plasma levels, RDR test)
- Pneumonia outcomes (e.g., disease severity, length of hospital stay, mortality rate, recurrence of infection)
- Vitamin A supplementation outcomes (dose, duration, effects)

6. Quality Assessment of Studies

The quality of the included studies was independently assessed using appropriate quality assessment tools for the study design (e.g., the Cochrane Risk of Bias tool for randomized clinical trials, and the Newcastle-Ottawa Scale for observational studies). The quality assessment was used to identify the strengths and weaknesses of the studies and to interpret the results in the context of the quality of the evidence.

7. Data Analysis and Synthesis

A descriptive analysis of the extracted data was performed to summarize the characteristics of the included studies and the main findings. The results were synthesized qualitatively, with a focus on consistent trends, contradictions, and gaps in the evidence. If the data were sufficiently homogeneous, a meta-analysis could be performed to estimate the overall effect. Special attention was paid to the reasons for the heterogeneity of the results among the studies, including differences in study design, population characteristics, vitamin A measurement methods, doses used in vitamin A supplementation, and socioeconomic and nutritional factors.

By following the PRISMA methodology, this review aims to provide a comprehensive and transparent assessment of the current evidence on the relationship between vitamin A, immunity, and the risk of pneumonia in children, with a focus on the latest studies and a critical analysis of the findings.

Results and Discussion

The results extracted from the reviewed studies confirm a clear relationship between vitamin A deficiency and pneumonia in children. The majority of studies indicated high rates of subclinical vitamin A deficiency in children with pneumonia, which supports the hypothesis that this vitamin deficiency may increase children's susceptibility to respiratory infections or affect the severity of the disease.

Causes of Discrepancy in Results and Identification of the Most Affected Age Groups:

It is interesting to note that some studies have indicated that the decrease in plasma vitamin A levels may be a result of the acute phase of the infection, as these levels were observed to rise after recovery or after receiving treatment. This suggests that the inflammation itself may affect the dynamics of vitamin A in the body, making the assessment of vitamin A status in sick children complex and requiring the use of more accurate indicators such as the Relative Dose Response (RDR) test, which reflects the vitamin A reserves in the liver.

Despite the evidence linking vitamin A deficiency to pneumonia, the effectiveness of vitamin A supplementation as an adjunct therapy for pneumonia is still under debate. Some studies have shown positive results, while other studies have not found a clear effect, or have even pointed to an increase in some symptoms. This discrepancy in the results can be attributed to several factors, including:

- Differences in study design: The studies varied in their methodologies, including sample size, inclusion and exclusion criteria, and methods of data collection and analysis. Studies with weak design or bias may lead to inaccurate or non-generalizable results.
- Baseline nutritional status of children: Children with underlying malnutrition or severe vitamin A deficiency may be the most likely to benefit from

supplementation, while children with adequate vitamin A levels may not show significant improvement.

- Severity of the disease: The response of children to vitamin A supplementation may differ based on the severity of their pneumonia. Children with acute pneumonia or complications

may benefit more from supplementation compared to mild cases.

- Doses of vitamin A used: The doses used in the studies varied significantly, and high doses may not be recommended as an adjunct therapy for lower respiratory tract infections. Determining the optimal dose is crucial to achieving the desired benefits without side effects.
- Potential interactions with other micronutrients: The effectiveness of vitamin A may be affected by the presence or absence of other micronutrients that play a role in immune function.
- Socioeconomic factors: Socioeconomic factors play a crucial role in determining the risk of vitamin A deficiency and susceptibility to pneumonia. Children from low-income families, who suffer from malnutrition, or who do not receive adequate breastfeeding, are more likely to be deficient in vitamin A and therefore more susceptible to severe pneumonia.

The Most Affected Age Groups and the Extent of Benefit from Supplementation:

Studies indicate that young children, especially those under two years of age, are the most affected age group by vitamin A deficiency and pneumonia. Children under two months of age and children over six months of age who are fed with industrialized milk may be at greater risk.

Regarding the extent of benefit from supplementation, the evidence suggests that vitamin A supplementation may be more beneficial in populations suffering from severe vitamin A deficiency or malnutrition. However, more research is still needed to determine the optimal dosage, timing of intervention, and target populations for vitamin A supplementation, taking into account the complex interaction between vitamin A status, immune response, and acute infection.

Overall, the findings indicate that vitamin A plays an important role in immunity against respiratory infections, and that its deficiency is common among children with pneumonia. However, more research is still needed to determine the optimal dosage and methods of administration for vitamin A supplementation as an adjunct therapy, in addition to a deeper understanding of the complex interactions between vitamin A and the immune response in the context of acute infection.

Conclusions

This review confirms that vitamin A deficiency is common among children with pneumonia, and that there is a correlation between low vitamin A levels and the severity of the disease. However, the direct causal relationship and the effect of vitamin A supplementation as an adjunct therapy require further research and clarification through well-controlled randomized clinical trials. Future research should focus on determining the optimal dosage, timing of intervention, and the groups most likely to benefit from vitamin A supplementation, taking into account the socioeconomic and nutritional factors that affect vitamin A status in children. It is also necessary to focus on a deeper understanding of the complex biological mechanisms that link vitamin A to immune function and the risk of pneumonia, and to more accurately identify the age groups most at risk, and to evaluate the effectiveness of supplementation in different contexts.

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