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THE IMPORTANCE OF KLEBSIELLA PNEUMONIAE IN COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN

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Abstract. In pediatric populations, pneumonia is a major source of morbidity and mortality, particularly in low- and middle-income countries (LMICs). It is crucial to understand the frequency and function of microorganisms in hospitalized pneumonia patients in order to guide diagnosis, treatment, and prevention strategies. The purpose of this review was to determine the prevalence of hospitalizations for pneumonia caused by *Klebsiella pneumoniae* in children under five in LMICs. Premature newborns now have a far higher survival rate because to ongoing advancements in medical technology. One of the most frequent bacteria that causes newborn infections is *Klebsiella pneumoniae* (*K. pneumoniae*), which poses a significant risk to preterm infants in particular. The purpose of this study was to examine the treatment results, antibiotic susceptibility profiles, and clinical features of *K. pneumoniae* infections in these neonates. In preterm newborns, K. pneumoniae isolates show significant infection prevalence, poor treatment results, and increased resistance. Our knowledge of K. pneumoniae infections and their relationship to clinical outcomes in preterm newborns is improved by these findings.The significant prevalence of *K. pneumoniae* in hospitalized pediatric pneumonia patients, especially in Asia, is highlighted in this analysis. In order to diagnose, treat, and prevent *K. pneumoniae*-associated pneumonia in pediatric populations, the results highlight the need for additional research, consistent criteria for grading pneumonia severity, and focused initiatives.

Keywords. Children, etiology, epidemiology, siderophores, *Klebsiella pneumoniae*, illnesses linked to healthcare.

Introduction. When dangerous microbes enter the lower respiratory tract—the region beneath the larynx—they can cause pneumonia. Aspiration, inhalation, and bloodstream transmission are some of the ways this invasion can happen. Pneumonia continues to be the primary infectious factor contributing to child mortality, especially in low- and middle-income countries (LMICs), and is the top cause of hospitalizations and deaths among children under the age of five globally. Pneumonia affected almost 138 million children under the age of five in 2015. 740,180 children died from pneumonia in 2019, accounting for 14% of all deaths in this age group. Although the majority of pneumonia-related deaths take place in LMICs, pneumonia also has a huge disease burden and high healthcare expenditures in wealthy nations. For example, with an estimated yearly incidence of 15.7 cases per 10,000 children and over 100,000 hospitalizations, pneumonia is a major cause of hospitalizations and outpatient visits for children in the United States. Children's pneumonia is caused by a variety of microorganisms, including bacteria, fungus, viruses, and other unusual creatures. Severe or extremely severe pneumonia is more likely to be caused by bacterial infections [1-5]. Bacterial pathogens like

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Klebsiella pneumoniae, Haemophilus influenzae and *Streptococcus pneumoniae* are very dangerous for newborns. Geographical location and certain illness circumstances may have an impact on the prevalence of these pathogens. *K. pneumoniae* accounts for 10% of all bacterial infections acquired in hospitals, making it the most common cause of pneumonia in healthcare settings. Children with pneumonia face a complicated and difficult disease landscape due to the significant pathogenic potential of many bacterial strains. Approximately 7% to 13% of pneumonia instances develop into severe pneumonia, which can cause damage and dysfunction in several organs, including the lungs. Concern over the rise of antibiotic-resistant forms of bacteria that cause pneumonia has grown. In order to guide immunization programs, empirical management techniques, and focused treatments, it is essential to regularly evaluate and apply the most recent data on the causes of childhood pneumonia [6-12]. A thorough examination of pneumonia linked to important pathogens in children is essential given the evolving epidemiology of infectious agents, especially in pediatric patients. Our goal in this systematic review was to calculate the prevalence of *K. pneumoniae*-associated pneumonia in children under five who are admitted to hospitals in low-income countries. Surprisingly, only about 31% of the research looked into the participants' nutritional status. Due to their weak immune systems and underdeveloped mucosal barriers, infants under the age of one are especially vulnerable to a variety of diseases. In a similar vein, children between the ages of one and three are particularly vulnerable because of the gradual development of their own immune systems and the decrease in maternal antibodies. The high heterogeneity across all subgroups ($I2 \geq 89\%$) further highlights the impact of several sources of inconsistency, which probably include variations in case definitions, pneumonia severity criteria, specimen types (e.g., blood vs. sputum), pre-hospital antibiotic use (reported in five studies), and diagnostic methods (most studies used PCR), all of which affect pathogen detection [13-19]. Because it followed the PRISMA principles, which guaranteed a methodical and open approach to the research, this review had a high level of credibility. To ensure that all pertinent research were included, extensive searches were carried out across various databases. A comprehensive examination of the topic was provided by the review, which also contained information on pneumonia coinfections involving bacteria, viruses, and fungi. A more thorough understanding of the subject was also made possible by the examination of associated risk factors in children with pneumonia, such as HIV and nutritional status. It is crucial to take into account the review's possible shortcomings, though. Studies with noteworthy or good results are more likely to be published, which could distort the overall conclusions and raise concerns about publication bias. Furthermore, depending solely on the literature that is currently accessible raises the risk of selection bias because some studies or geographical areas may be overrepresented while others may be underrepresented. The results' generalizability and comparability may be impacted by the heterogeneity among the included studies, which includes differences in study design, case definitions, antibiotic exposure prior to specimen collection, and diagnostic techniques [20-28].

The cause of pediatric pneumonia is evolving. *Staphylococcus aureus* and *Klebsiella pneumoniae* were linked to some severe cases, but *S. pneumoniae* and *H. influenzae type B* were shown to be the most significant bacterial causes of pneumonia in a comprehensive analysis of etiology studies conducted before new conjugate vaccines became available. The most common viral cause of pneumonia, found in 15–40% of cases, was respiratory syncytial virus, which was followed by influenza A and B, parainfluenza, human metapneumovirus, and adenovirus. More recent meta-analyses of etiology data point to a shifting pathogen profile, with a growing understanding that several organisms interact sequentially or concurrently to generate clinical pneumonia. In instance, several infections frequently produce severe disease.

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Viral diseases are becoming more common due to widespread vaccination against pneumococcal conjugate and *Haemophilus influenzae type B* conjugate. According to recent case-control studies, viruses were found in 81% of radiologic pneumonia cases in Sweden and at least one virus in 87% of clinical pneumonia cases in South Africa [4-12]. Similar to this, Mycobacterium tuberculosis has been identified as a pathogen in acute pneumonia in children residing in high tuberculosis-prevalence settings, and childhood tuberculosis is a significant cause of morbidity and mortality in many low- and middle-income nations. *M. tuberculosis* has frequently been detected in postmortem examinations of children who died from acute respiratory disease. About 8% of instances of pediatric pneumonia were found to have culture-confirmed tuberculosis, according to a recent systematic review. Since only a small percentage of cases of intrathoracic tuberculosis disease are confirmed by culture, the true burden may be substantially greater. As a result, tuberculosis may have a significant role in the incidence and death of childhood pneumonia in high-prevalence areas [14-21].

A complicated interplay between host and environmental risk factors leads to childhood pneumonia and clinically severe illness. Incomplete or insufficient immunization must be regarded as a significant preventable risk factor for children pneumonia due to the efficacy of pneumococcal conjugate vaccination and Haemophilus influenzae type B conjugate vaccine in preventing radiologic and clinical pneumonia. Additional risk factors include low birth weight, which is linked to 1.8 times higher odds of severe pneumonia in high-income nations and 3.2 times higher odds in low- and middle-income countries.In a similar vein, the odds of severe pneumonia are increased by 2.7 times in low- and middle-income countries and 1.3 times in high-income countries if exclusive breastfeeding is not provided for the first four months of life. The danger of household crowding remains constant, with odds ratios ranging from 1.9 to 2.3 in both high-income and low-income nations. Lack of measles vaccination by the end of the first year of life raises the risk of pneumonia by 1.8 times, while indoor air pollution from the use of solid or biomass fuels increases the risk by 1.6 times. According to estimates, between 2000 and 2010, the prevalence of these important risk factors dropped by 25% in low- and middle-income countries, which helped lower the incidence and mortality of pneumonia in these nations, even in those without conjugate vaccines. HIV infection, which is particularly common among children in sub-Saharan Africa, is the single biggest risk factor for pneumonia. HIV-positive children are six times more likely than HIV-negative children to get severe pneumonia or to die [5-12]. Since mother-to-child HIV transmission has been effectively prevented, the number of uninfected children who have been exposed to HIV is increasing; their excess risk of pneumonia has been reported to be 1.3–3.4 times higher than that of children who have not been exposed to HIV [13-17].

Both the *Haemophilus influenzae type B* conjugate vaccination and the pneumococcal conjugate vaccination have proven to be useful in reducing the incidence, severity, and mortality of pneumonia. Equitable vaccination coverage and access, however, are still not at their best. By the end of 2015, 73 countries have implemented the conjugate vaccination against *Haemophilus influenzae type B,* with an estimated 68% global coverage. Regional disparities still exist, though: coverage is predicted to be 90% in the Americas and only 25% in the Western Pacific. By 2015, 54 countries had implemented pneumococcal conjugate vaccination, and 35% of the world's baby populations had received three doses of the vaccine. The World Health Organization's Global Vaccine Access Plan effort was started to address this problem by increasing the equitable availability of life-saving immunizations [11-18]. The program's goals include securing guarantees for vaccine financing, strengthening health systems, encouraging

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pertinent local research and development innovations, social marketing to individuals and communities, and fostering political will in low- and middle-income countries to prioritize immunization. It has been demonstrated that maternal vaccination against pertussis, influenza, and tetanus is effective in preventing illness in the youngest infants. Pregnancy-related influenza vaccination is safe, gives mothers a reasonable level of protection against influenza, and temporarily shields infants from confirmed influenza infection (vaccine effectiveness 63% in Bangladesh and 50.4% in South Africa). However, baby protection does not last much longer than eight weeks after delivery due to a significant decline in antibody levels. A phase-3 clinical trial to determine the effectiveness of respiratory syncytial virus vaccination in preventing respiratory syncytial virus disease in infants is currently underway, and it has recently been demonstrated to be safe and immunogenic during pregnancy. Pneumonia incidence, morbidity, and death may further decline within ten years if the respiratory syncytial virus in infancy can be prevented by vaccination. Further reductions in the prevalence of childhood pneumonia may be facilitated by better living conditions, better nutrition, and easier access to healthcare. Numerous opportunities to protect, prevent, and treat children are highlighted in the WHO Integrated Global Action Plan for pneumonia and diarrhea [1-8]. Programs that combine teaching and counseling interventions in homes, communities, and healthcare institutions, as well as the promotion of baby-friendly hospitals, can increase breastfeeding rates. Reducing exposure to cigarette smoke, using cleaner cooking fuels, and improving house ventilation are crucial treatments to lower the frequency and severity of pneumonia. By offering therapies to stop mother-to-child transmission, pediatric HIV can be prevented. The incidence of community-acquired pneumonia in children with HIV infection can be significantly decreased by early newborn HIV testing, early antiretroviral medication initiation, and cotrimoxazole prophylaxis. Improved care-seeking behavior is an indirect result of community-based initiatives that lower pneumonia mortality. It is anticipated that by 2025, 67% of pneumonia deaths in low- and middle-income countries might be avoided if these affordable therapies were expanded [20-27].

A method for classifying the severity of pneumonia as either severe or non-severe is called case management. Parenteral antibiotics are recommended for severe instances, and all children receive early, appropriate oral antibiotics. Case management as part of Integrated Management of Childhood Illness was linked to a 27% reduction in overall child mortality and a 42% reduction in pneumonia-specific mortality when it was used in high-burden areas prior to the availability of conjugate vaccinations. However, the low case fatality rate and preponderance of viral causes of pneumonia have raised concerns about antibiotic usage. For non-severe pneumonia, a number of randomized controlled trials comparing oral antibiotics to placebo have been conducted. The results of antibiotic and placebo treatments were comparable in two investigations conducted in Denmark and India. In the third study conducted in Pakistan, the placebo group was found to be non-equivalent to the antibiotic group due to a non-significant 24% vs. 20% failure rate. Furthermore, many children with clinical pneumonia may actually have viral bronchiolitis, for which medicines are ineffective, since WHO-classified non-severe pneumonia and bronchiolitis may be seen as a spectrum of lower respiratory disease [5-11]. According to national pneumonia guidelines in Spain and Britain, children under the age of two who exhibit non-severe pneumonia and have evidence of pneumococcal conjugate vaccination are not advised to receive standard antibiotic treatment. According to national guidelines in the United States, children with non-severe pneumonia up to the age of five should not be given antibiotics. However, the updated World Health Organization pneumonia guidelines still advise antibiotic treatment for all children who meet the WHO pneumonia case

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definitions due to the high mortality from pneumonia in low- and middle-income countries, the difficulty in accessing care, and the high prevalence of risk factors for severe disease. It is projected that the use of supplementary oxygen systems could reduce the mortality of children with hypoxic pneumonia by 20%. supplementary oxygen is life-saving, but it is not always available in low- and middle-income countries. The top 15 priorities for future childhood pneumonia research include determining the systems' capacity to boost oxygen availability in medical facilities and identifying obstacles to further implementation. However, up to 81% of pneumonia deaths in 2010 happened outside of medical facilities, indicating significant issues with vulnerable groups' health-seeking behavior and access to healthcare resources. The life and well-being of the most vulnerable children may be impacted by identifying and removing obstacles to receiving medical care [21-28].

Discussion. The estimated percentage of cases linked to *K. pneumoniae* was 5% (95% CI: 2%–8%; I 2 = 98%) based on the meta-analysis of 61,030 hospitalizations for pneumonia in children under 5 from the 16 included studies. With a statistically significant subgroup difference (p = 0.035), stratification by World Bank categorization revealed a substantially larger pooled proportion in the upper-middle-income nations (7%) compared to the lower-middle-income countries (4%) and low-income countries (1%). This paradoxical gradient, where a greater burden is seen in comparatively wealthier LMIC settings, could be the result of variations in case definitions, healthcare access, diagnostic capabilities, or past antibiotic usage patterns. While low-income settings may rely more heavily on culture-based methods with lower sensitivity, particularly after pre-hospital antibiotic administration, upper-middle-income countries frequently have more robust laboratory infrastructure and broader use of molecular diagnostics (e.g., PCR), which may improve the detection of *K. pneumoniae*. Furthermore, in more established LMIC situations, variations in vaccination coverage (e.g., for *S. pneumoniae* and *H. influenzae type b*) may change the relative contribution of diseases like *K. pneumoniae*. In particular, the pooled fraction was significantly greater in Asia (6%; 95% CI: 1%–10%) than in Africa (3%; 95% CI: 1%–5%) [5-11]. This result is consistent with more general epidemiological patterns indicating that Asian pediatric populations have a greater burden of Gram-negative bacteria. perhaps impacted by variations in diagnostic capabilities, antibiotic use trends, and healthcare infrastructure. Furthermore, seasonal fluctuations—especially in the winter—are linked to a rise in pediatric pneumonia, which can be impacted by elements including temperature, humidity, and indoor congestion. Nevertheless, the findings showed that none of the research assessed how seasonal and environmental factors affected pneumonia. Furthermore, even with antiretroviral medication, pneumonia is still a frequent side effect among HIV-positive people. Remarkably, only 25% of the studies—all carried out in Africa, where HIV prevalence is high—looked at the connection between HIV and pneumonia. In developing nations, malnutrition has been found to be a major risk factor for childhood pneumonia. The observed heterogeneity was also probably influenced by variations in vaccine coverage against S. pneumoniae and H. influenzae type b, as well as unmeasured factors such HIV prevalence, malnutrition, and local antibiotic resistance trends. The symptoms of pediatric CAP in previously healthy children are brought on by infections contracted outside of a hospital. According to our assessment, severe episodes of pneumonia were frequent and the majority of cases happened in the community. Crucially, *S. aureus, H. influenzae* and *S. pneumoniae* infections often coexist with *K. pneumoniae* infections, and viral agents such RSV and adenoviruses are also frequently involved [12-18]. Usually present in the intestinal and respiratory tracts, *K. pneumoniae* can cause infections by taking advantage of weaknesses in the immune system or during invasive treatments. Because this review followed the PRISMA

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principles, which guaranteed a methodical and open approach to the research, it had a high degree of credibility. To ensure that all pertinent research were included, thorough searches were carried out across key databases. A comprehensive examination of the topic was provided by the review, which also contained information on pneumonia coinfections involving bacteria, viruses, and fungi. A more thorough understanding of the subject was further aided by the examination of associated risk factors in children with pneumonia, such as HIV and nutritional status. Nonetheless, it is crucial to take into account this review's possible shortcomings. Because research with noteworthy or good results are more likely to be published, publication bias may be an issue, potentially distorting the overall conclusions. Furthermore, depending solely on the literature that is currently accessible raises the risk of selection bias because some studies or geographical areas can be overrepresented while others might be underrepresented. The generalizability and comparability of the results may be impacted by the heterogeneity among the included studies, which includes differences in study design, case definitions, antibiotic exposure prior to specimen collection, and diagnostic techniques [21-28].

Conclusions. The important significance of *K. pneumoniae* in CAP is highlighted by this pilot investigation, which also shows that tNGS and culture-based diagnostics capture different but complimentary features of its identification and resistance profiling. Compared to pure *K. pneumoniae* cultures, direct sputum tNGS showed a wider resistome and more microbial diversity. In contrast, classical methods remain essential for species confirmation, phenotypic susceptibility testing, and clinical decision-making. Crucially, tNGS enhances culture-based processes rather than replaces them; careful interpretation is required due to its targeted design and incapacity to differentiate between viable and non-viable organisms. The most reliable framework for enhancing pathogen detection, directing antimicrobial therapy, and bolstering AMR surveillance in *K. pneumoniae*-associated CAP is provided by an integrated diagnostic strategy that combines culture, MALDI-TOF MS, DDM, and tNGS, with potential addition of viability-discriminating techniques.

The number of childhood pneumonia-related mortality has significantly decreased. The incidence and severity of childhood pneumonia have significantly decreased as a result of improved socioeconomic level and vaccinations, particularly the conjugate vaccines (against *Haemophilus influenzae* and pneumococcus). HIV-related pneumonia deaths have decreased as a result of improved HIV prevention and management techniques. However, there are still disparities in access to care and the availability of effective interventions, particularly in low- and middle-income nations, despite significant changes in incidence, etiology, and radiology worldwide. For the residual burden of pediatric pneumonia, new interventions must be created and effective ones must be made more broadly accessible.

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