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Precision Risk Stratification Analyses and Measures of Respiratory Infections

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Abstract. Respiratory tract infections are one of the leading causes of morbidity and mortality worldwide, with particularly significant disease burden in specific vulnerable populations, such as young children, older adults, and patients with chronic respiratory diseases. These groups serve as the high-risk populations for respiratory tract infections and their disease characteristics, risk factors, and prevention need exhibit distinct differences. For example, young children show higher viral infection rates, while older adults face greater risks from comorbidities. Most existing studies focus on a single population or a specific virus, lacking a systematic review across populations to identify overlooked similarities and differences. This study systematically synthesizes the epidemiological characteristics, key risk factors and management strategies for respiratory tract infections from recent studies in these three high-risk populations. This study may provide insights for understanding the disease characteristics of different populations, optimizing prevention and control practices, and inspiring future research on antibiotics, vaccines, and related interventions.

Keywords: Respiratory Tract Infections, Management Strategies, Respiratory Syncytial Virus, Pathogens, Chronic Respiratory Diseases.

1. Introduction

Respiratory tract infections (RTIs) are a major public health problem and have been recognized by the World Health Organization (WHO) as a leading cause of morbidity and mortality worldwide. Key high-risk populations include premature infants, children aged 6 months to 5 years, adults aged 65 and above, and patients with chronic respiratory diseases. The main pathogens for these groups are the respiratory syncytial virus and influenza virus. Among them, children under 5 years of age are particularly vulnerable. In developing countries, 30% of deaths in children under 5 years of age are due to respiratory infections [1]. Surviving infected children may face long-term respiratory problems. Additionally, the costs of long-term treatment and health management may lead to an economic burden on families. Previous studies have shown that the burden of respiratory infections have a particularly severe impact on the mentioned specific age groups and there are significant differences between regions with different resource conditions. This is mainly due to the differences in access to preventive tools, diagnostic abilities, and the level of targeted intervention measures [2].

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This study focuses on children under 5 years of age while also including older adults and patients with chronic respiratory diseases as comparison populations. From a theoretical perspective, this work addresses a critical gap in the characterization of combined risk analysis among high-risk pediatric subgroups. It also establishes a cross-population analysis, which is lacking in the existing literature. For public health policy, systematically analyze the infection transmission patterns, high-risk scenarios, and controllable risk factors among different populations, providing a basis to develop precise prevention and control strategies.

2. Risk and disease burden analysis on young children

2.1. Infections risk profiles and vulnerability patterns

2.1.1. RSV infection progression and hypoxemia as a severity indicator

In children under 5 years of age, the acute severity and long-term respiratory sequelae of respiratory syncytial virus (RSV) infection follow a sequential causal pathway based on early-life developmental vulnerability. Specifically for infants, almost all of them face their initial RSV infection before 2 years old. Although they can obtain RSV-specific antibodies from their mothers, these antibodies gradually decrease over the first month of their lives. During the process of maternal antibody reduction, infants are more likely to be infected with an upper respiratory tract infection. A 2025 study indicated that HNO-ALIs from children showed an elevated inflammatory cytokine response, mucus production, increased cell damage, limited regeneration of ciliated cells, and limited mucociliary cleaning function. Therefore, they inferred that the inability to control the upper respiratory tract in infants can lead to lower respiratory tract infection (LRTI) [3]. Severe LRTI can result in significant hypoxemia, respiratory muscle fatigue, and even death. RSV infection may progress to LRTI. A retrospective study on RSV infection in children with LRTI under two years in Colombia showed that 57.5% of them had hypoxemia, indicating that hypoxemia can serve as an indicator of acute infection severity in children with LRTI.

From the perspective of long-term disease risk, a study in Australia found that RSV infection before the age of 2 significantly increases the risk of asthma, wheezing and other respiratory diseases requiring medical intervention in children after the age of 2. The core reason underlying this phenomenon is that the adaptive immune system of children under 5 years of age is not yet mature. RSV infection in infants can disrupt the formation of antiviral immune memory, trigger persistent respiratory inflammation, and affect the underdeveloped respiratory tissues, leading to structural remodeling, thereby increasing the long-term risk of chronic respiratory diseases [4].

2.1.2. Global infection risk for different regions

From the Figure 1, it is suggested that the high burden is always in regions with limited healthcare resources. These regions probably lack complex pathogen detection equipment. Compared with experimental equipment used for detecting specific pathogens, Hypoxemia is commonly assessed using a pulse oximeter, which is easier to operate and has a cheaper cost. Thus, hypoxemia, serving as a simple detection indicator, can play a pivotal role in helping the local area to quickly determine the severity of the infection.

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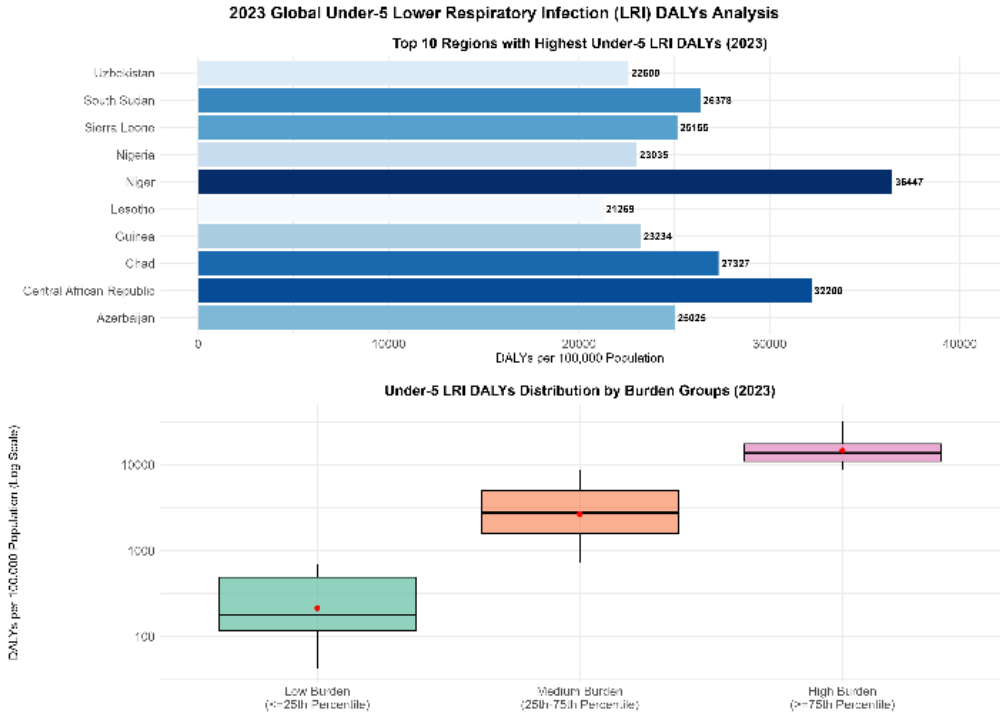

Figure 1. Global burden of acute lower respiratory infections in children under 5 years of age, 2023. Data is from Global Burden of Disease (GBD) 2023

2.2. Bacterial pathogens and disease progression pathways in pediatric respiratory infections

Respiratory infections in young children are primarily caused by bacterial and viral pathogens. Bacterial pathogens represent major contributors to respiratory infections in young children and are responsible for a substantial proportion of severe cases and complications. Among these pathogens, Streptococcus pneumoniae is one of the most important causes of lower respiratory tract infections and invasive disease in children under five years of age. This pathogenic pathway had been specifically adapted and was strongly supported by epidemiological data in children. The disease progression begins with asymptomatic colonization of the nasopharynx. This step has been confirmed as a necessary step in both Lithuania's research and Ethiopia's study. In these two studies, the nasopharyngeal colonization rate among children with acute respiratory infections was as high as 40.8% and 18%, respectively [5,6]. The research of Lithuania highlighted a key characteristic of a specific pathogen, which is that there are differences in virulence among different serotypes. Their analysis found that dominant serotypes, such as 6B, 19F, and 23F, which are common among children under 6 years old, have a stronger ability to transition from colonization to invasive disease.

This transformation does not occur randomly but is triggered by specific host and environmental risk factors, which have been confirmed in the research group from Ethiopia. Poor indoor ventilation, non-breastfeeding, and a history of upper respiratory tract infection were found to significantly disrupt the mucosal barrier, allowing bacteria to invade the lower respiratory tract. Once these bacteria establish themselves in the alveoli, a strong inflammatory response can be triggered, leading to thickening of lung tissue. This was demonstrated in a study in Ethiopia, where these strains showed significant resistance to co-trimoxazole and tetracycline [6]. The impact of this pathogenic pathway will be more persistent, and then increase the likelihood of disease progression.

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The complications caused by this specific infection pathway are directly related to the bacteria's tendency to invade and the virulence of the serotype.

Among infants, the main serotypes associated with a high colonization rate can cause invasive pneumococcal disease (IPD), which is the most severe type of complication [5]. This includes bacteremia and meningitis, which are more common in vulnerable children under 5 years of age. On the other hand, during the initial stage of the pathogenic chain, which is the colonization in the nasopharynx and upper respiratory tract infections, it usually leads to non-invasive complications such as acute otitis media and sinusitis. Those are extremely common in this age group due to the immature anatomy. Also, the presence of antibiotic resistance further increases the risk of severe complications, since it makes the inflammatory stage longer in the pathogenic chain.

2.3. Effectiveness of precision prevention and management strategies

RSV infection exerts long-term effects on the body, including impaired lung function, recurrent wheezing, and asthma. To minimize the negative impact of this disease on children, timely vaccination and preventive measures are crucial. Maternal RSV vaccination and long-acting monoclonal antibody (Nirsevimab) are strongly recommended as core prevention strategies by WHO, as they can significantly reduce the risk of hospitalization and severe illness from RSV infection in young children [7]. In resource-limited regions with the highest disease burden, hypoxemia via pulse oximetry should be a more practical indicator to reduce missed diagnosis and misdiagnosis of the disease.

Furthermore, government support, including expanded medical insurance coverage and reduction of out-of-pocket medical costs, is essential to alleviate the economic burden on families of children with RSV infection. With ongoing advances in medical research and development, RSV will gradually be brought under control.

3. Analysis of older adults

3.1. Demographic and clinical profiles

The older adults with ARI in both community-dwelling and long-term care facility have demographic characteristics and clinical features, including age distribution, gender differences, comorbidities, and pathogen profiles.

Age is one of the core factors influencing incidence and severe outcomes in older adults. Much research data of older adults confirms that increasing of age is significantly positively correlated with the risk of ARI infection. Trucchi et al. in 2019 found that the overall incidence rate of influenza-like illness (ILI) and LRTI continues to increase with age. Particularly in the adults ≥85 years, the incidence rate is 18.92 per 1000 person-years [8]. Secondly, gender differences may lead to differences in the incidence rate of ARI among older adults by influencing health care-seeking behavior. A study in a community cohort indicated that in adults ≥50 years old, females had higher seasonal incidences of RSV, RSV A, and RSV B than males, though the 95% confidence limits overlapped. For example, the seasonal incidence of RSV was 178 per 10,000 in females and 127 per 10,000 in males, with 95% confidence limits (147, 216) and (99, 163) respectively. These proved that gender differences are not due only to ARI [9].

For respiratory symptoms, cough, fever and rhinorrhoea were the most common among influenza-positive ARIs to older adults. Of note, the study demonstrated that in season 2, fever was found to be less common [9]. Therefore, diagnosing ARI based only on 1 or 2 symptoms probably

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leads to a missed diagnosis. This makes clarifying the pathogen profiles crucial for accurate diagnosis. RSV is a major pathogen for respiratory infections in older adults. A 2022 prospective cohort study in Japan used a multiplex polymerase chain reaction to detect pathogens in nasopharyngeal swabs of acute respiratory disease (ARD) patients, aiming to evaluate the incidence rate of ARD in older adults over 52 weeks. They concluded that RSV, influenza A/H1, and human metapneumovirus (HMPV) were the major respiratory pathogens leading to ARI [10]. The result is highly consistent with a global Meta-analysis. The virus-specific attributable fraction among the exposed (AFE) of RSV, flu, and HMPV were 88%, 88%, and 90%, indicating a significant impact on the incidence rate of ARI in older adults [2]. Finally, comorbidities are relatively common in older adults with ARI, which is a core factor contributing to severe infection. Of the older adults with ARI, 42.66% had at least one comorbidity. The detailed prevalences were 23.49% in 50-54, 44.19% in 65-69 and 59.92% in 80-84, showing an increasing trend with age [8]. This highlights the importance of recognizing comorbidity for older adults.

3.2. Risk factors

For general older adults, risk factors of respiratory infection include age, underlying diseases and economic status. Research in rural north India showed that higher age, pre-existing chronic bronchitis, other pre-existing co-morbidities, and poor household income were risk factors for LRTI. The detailed incidence rate ratio of persons with pre-existing chronic bronchitis, compared to those without, was 4.7 [11]. Another study indicated that chronic heart failure class II and diabetes requiring insulin treatment were the risk factors of ARI in older adults. Furthermore, females may also be a risk factor, though a confirmed explanation remains unknown [9].

3.3. Disease severity and outcomes

The severity of respiratory infections has a significant influence on clinical outcomes and disease burden. Firstly, advanced age itself significantly amplifies the severity of respiratory infections and directly increase the risk of death in patients. A Cross-Sectional Study with RSV in Spain from 2016 to 2023 evaluated risk factors for death by multivariable logistic regression and found that age is the main factor. Of the patients over 80 years of age, in-hospital mortality was as high as 8.9%, not only greater than the average level of the population in the study but also over the range of international RSV infection rates [12]. That confirms that very old adults have higher disease severity and worse clinical outcomes.

Secondly, underlying comorbidities interact with advanced age and the severity of RSV infection, causing a further increase in the risk of adverse clinical outcomes. Although advanced age itself contributes to immune aging and organ dysfunction, which already increases the risk of severe disease and death from RSV infection, underlying comorbidities then build on this foundation to further accelerate RSV disease progression. Of note, the two factors together amplify the adverse impact and serve as a key driver of worse clinical outcomes. The Spanish study also confirmed that underlying comorbidities are independent risk factors for RSV-related in-hospital mortality in this very elderly (≥80 years) population. Specifically, severe renal insufficiency (defined as glomerular filtration rate [GFR] <38 mL/in/m^2) showed the strongest association with RSV-related in-hospital mortality, exhibiting a significantly higher risk of in-hospital death (OR=4.92, 95% CI 1.55–15.63, p=0.001). Similarly, comorbid cerebrovascular disease showed a significant increase in mortality risk (OR=5.43, 95% CI 1.23–13.73, p=0.029) [12]. These underlying comorbidities not only independently increase the risk of fatal RSV infection but also show a synergistic effect with the risk

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from advanced age, which worsens RSV disease progression and then leads to higher healthcare resource consumption.

Thirdly, the increase in the severity of the disease directly leads to an increase in the consumption of medical resources, thereby causing a heavy burden on the medical economy. Combined with the study in Spain, renal failure for older adults not only increases the hospital mortality of RSV infection but also may lead to more consumption of medical resources. That indicates that increased disease severity often translates into prolonged hospitalization, higher likelihood of intensive care admission, and greater need for organ support therapies, thereby substantially increasing healthcare expenditures. Specifically, a study demonstrated that the cost of ED accesses and hospitalizations was €3593 for older elderly and reached €3900 for renal failure and cancer risk groups [8]. Overall, disease severity in elderly populations not only determines survival outcomes but also substantially increases economic burden, highlighting the importance of early risk stratification and preventive strategies.

3.4. Management strategies

In summary, for weakened immunity and often suffering from underlying diseases in older adults, once an infection occurs, the progression can be very rapid and may not be controllable. Therefore, the development and implementation of individualized, cycle health management plans are the core guarantee for older adults to achieve precise intervention of risk factors and continuously improve management effectiveness.

Infection prevention should take comprehensive geriatric assessment as its core foundation. On one hand, the core of its management is about the prevention and control of major geriatric syndromes, including routine frailty screening and multidisciplinary intervention, early identification and intervention of cognitive impairment, as well as fall risk stratification and comprehensive prevention. On the other hand, vaccination against respiratory pathogens, full implementation of basic infection prevention and control measures such as hand hygiene and home environment protection, and steady-state management of chronic underlying diseases jointly build an active immune barrier, protect the immunity, and minimize the risk of infection exposure in the elderly.

For older adults at high risk with impaired immunity and chronic underlying diseases who develop acute respiratory tract infection, the core goals of acute period management are to control rapid infection, prevent disease progression, protect organ function, and reduce mortality risk. The principle of individualized medication for older adults must be executed throughout the entire treatment course, accompanied by synchronous multidisciplinary comprehensive intervention. For medication safety management, the principle of individualized medication for older adults must be strictly followed. Firstly, the medication regimen should be simplified during the acute periods, with priority given to address the core targets such as infection control, airway management, and management of acute exacerbation of underlying diseases. Secondly, drug dosages should be dynamically adjusted according to the patient's hepatic and renal function. Finally, inappropriate medications for the elderly should be avoided throughout the treatment to minimize the risk of adverse reactions.

After acute respiratory tract infection control, older adults still face risks of functional decline, underlying disease progression and recurrent infection. The core of chronic period management is to form a full-cycle management through long-term standardized comprehensive geriatric management. Firstly, standardized chronic disease regimens are developed to keep core indicators up to standard and maintenance treatment for chronic airway diseases should be strictly regulated.

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Secondly, regular medication reconciliation is conducted through comprehensive geriatric assessment to ensure long-term medication safety and efficacy. For home-based care support, it is necessary to promote age-friendly home environment changes, standardized home nursing services, systematic training and social support for caregivers.

Comprehensive, individualized, and multidisciplinary management is essential to mitigate the heightened vulnerability of older adults to respiratory infections and their sequelae.

4. Respiratory infection risk in patients with chronic respiratory diseases

4.1. Population characteristics and baseline vulnerability

The risk of respiratory infection in patients with chronic respiratory diseases (CRD) shows variability, depending on specific population characteristics and base line risk factors. Chronic obstructive pulmonary disease (COPD) is a core high-risk disease. Structural airway remodeling, impaired mucociliary clearance, and chronic inflammation in COPD create a permissive environment for viral and bacterial colonization. Research from First Affiliated Hospital of Soochow University indicated that among 154 CRD patients, COPD was the most prevalent disease (44.2%, 68/154). Thereby, COPD patients became the group at high risk of secondary LRTI [13]. Furthermore, the Danish Register of COPD confirmed that the degree of pulmonary impairment is positively related to the risk of infection for middle-aged and elderly individuals. Specifically, patients with severe airway obstruction (FEV1 < 30%) accounted for 15.5%, and their infection risk was significantly higher than that of patients with slight airway obstruction [14]. Another important vulnerable group is patients with bronchiectasis. The persistent and irreversible dilation of the bronchia increase their vulnerability to recurrent infections [15].

4.2. Adverse clinical outcomes of respiratory infections

After a respiratory infection, patients with CRD are likely to develop an acute exacerbation of their condition, which can be severe or even fatal, as well as long-term irreversible harm.

In the acute period, infection is the main trigger for the disease exacerbation. Mulpuru S et al. concluded that among 3931 hospitalized patients with COPD, respiratory viral infection was associated with a higher risk of ICU admission (OR 1.5, 95% CI 1.2–1.9) and increased need for mechanical ventilation (OR 1.9, 95% CI 1.4–2.5) [16]. The severity depends on the virus. In terms of non-invasive ventilation requirement, patients with RSV infection had 3.5-fold higher odds than those with influenza infection (95% CI 1.82–5.11) [16].

In the long term, infections can accelerate the irreversible progression of chronic diseases. Viral infection affects the expression of the interferon-related genes in bronchial epithelial cells, which is negatively associated with the severity of disease as measured by FEV percent predicted value [17]. For individuals with a history of early-life RSV infection, airway developmental abnormalities caused by the virus persist long term. This persistence interacts with genetic susceptibility, immune function changes, and exposure to childhood environmental tobacco smoke, resulting in the promotion of chronic respiratory diseases. In adulthood, smoking further exacerbates airway obstruction, accelerating the irreversible progression of chronic respiratory diseases [17]. Thus, respiratory infections not only trigger acute exacerbations but also contribute to irreversible disease progression in CRD patients.

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4.3. Management efficiency

Preventive management and optimization of basic disease management are crucial components for management efficacy.

For preventive management, influenza vaccination has been shown to significantly reduce influenza-related hospitalization rates in patients with COPD. In a large cohort study enrolling 4198 hospitalized COPD patients with known vaccination status, influenza vaccination was associated with an adjusted 38% reduction in the risk of influenza-related hospitalizations compared with unvaccinated counterparts. Meanwhile, influenza infection is a critical driver of adverse clinical outcomes in COPD patients: influenza-positive individuals had significantly higher crude mortality (9.7% vs 7.9%, P = .047) and critical illness incidence (17.2% vs 12.1%, P < .001) than influenza-negative patients [18]. These findings highlight that improving influenza vaccination coverage can effectively reduce the risk of severe disease and hospitalization in this susceptible population.

For the optimization of basic disease management, the use of inhaled corticosteroids (ICS) requires careful dosage consideration. A study of COPD patients demonstrated that a dose-dependent increased risk of Moraxella catarrhalis detection in lower respiratory specimens among ICS users compared to non-users. Specifically, the hazard ratios were 1.65 for low-dose, 1.82 for medium-dose, and 2.80 for the highest-dose ICS, with all p-values indicating statistical significance. Sensitivity analyses confirmed the stability of these findings, and consistent results were observed in 87% of patients who met clinical infection criteria [14]. This suggests that during acute exacerbation management, doctors should weigh the anti-inflammatory benefits of ICS against the potential increased risk of Moraxella catarrhalis infection, particularly when using higher doses

5. Limitation and strengths

Of the patients with respiratory infection, existing studies mostly focus on the risk of single type of infection. There is a lack of precise stratified analysis of different subtypes of infection and research on differential prevention for patients with different severities. For older adults, the burden analysis of respiratory infections is always limited to macro-indicators such as hospitalization rates, but research on micro-burdens such as decreased quality of life and increased long-term care needs is insufficient. In future, more studies may focus on stratified analysis of different respiratory infection subtypes in different populations

6. Conclusion

This review study systematically summarizes respiratory infections' characteristics, risk factors, and management strategies for young children, older adults, and patients with chronic respiratory diseases. The existing studies lack stratified analysis by population and micro-level burden assessment. Future research could focus on precise prevention and individualized strategies.

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