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2734 17 Avenue SW,  
Calgary, Alberta, T3E0A7,  
Canada  
+15878858911  
editorial-office@sciformat.ca

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RESPIRATORY SYNCYTIAL VIRUS INFECTION IN PATIENTS WITH RHEUMATOID ARTHRITIS: DOES DISEASE STATUS AND IMMUNOSUPPRESSION ALTER CLINICAL COURSE, SEVERITY, AND HOSPITALIZATION RISK?

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# RESPIRATORY SYNCYTIAL VIRUS INFECTION IN PATIENTS WITH RHEUMATOID ARTHRITIS: DOES DISEASE STATUS AND IMMUNOSUPPRESSION ALTER CLINICAL COURSE, SEVERITY, AND HOSPITALIZATION RISK?

**Szymon Antoni Kaźmierczak** (Corresponding Author, Email: [kazmierczakszymek@gmail.com](mailto:kazmierczakszymek@gmail.com))  
Wolski Hospital in Warsaw, Marcina Kasprzaka 17, 01-211 Warsaw, Poland  
ORCID ID: 0009-0004-3678-5126

**Natalia Sobieska**  
Akademia Leona Koźmińskiego, Warsaw, Mazovia, Poland  
ORCID ID: 0009-0007-5271-5322

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## ABSTRACT

Respiratory syncytial virus (RSV) is an increasingly recognized cause of severe respiratory infection in older adults, particularly those with underlying comorbidities and immunosuppression. However, the specific burden of RSV disease in patients with rheumatoid arthritis (RA) and other systemic autoimmune rheumatic diseases (SARD) remains incompletely characterized. This narrative review synthesizes current evidence on RSV epidemiology in immunocompromised populations, pathophysiological mechanisms underlying increased susceptibility in RA, risk stratification approaches, clinical presentation and complications, prevention strategies including recently approved vaccines (Arexvy, Abrysvo, mResvia), and clinical management recommendations. Recent data demonstrate that RA patients have substantially higher hospitalization rates (approximately 54%) compared with immunocompetent older adults (6–8%), with frailty emerging as the strongest independent predictor of severe infection (adjusted odds ratio 5.15). Contemporary evidence supports the benefit of RSV vaccination in older adults; however, reduced immunogenicity has been documented in patients receiving targeted immunosuppressive therapies. This review emphasizes individualized risk assessment, optimization of immunosuppression, timely vaccination with enhanced monitoring in high-risk subgroups, early clinical recognition of RSV infection, and evidence-based management approaches. By integrating clinical epidemiology with preventive and therapeutic strategies, contemporary practice can substantially reduce RSV-related complications in this vulnerable population.

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## KEYWORDS

Respiratory Syncytial Virus, Rheumatoid Arthritis, Immunosuppression, Viral Infection, Risk Stratification, Vaccination, Clinical Outcomes, Hospitalization, TNF Inhibitors, Disease-Modifying Antirheumatic Drugs

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## Introduction

Respiratory syncytial virus (RSV) causes significant respiratory disease across age groups, but disease severity increases substantially in older adults and immunocompromised patients [1]. For decades, RSV was considered primarily a pediatric pathogen, but contemporary surveillance and epidemiological data have demonstrated that RSV is responsible for substantial morbidity and mortality in community-dwelling and institutionalized older adults [2]. RSV hospitalizes approximately 50,000 to 160,000 individuals annually in the United States, with mortality rates ranging from 2% to 4% in hospitalized patients and higher rates in frail and severely immunocompromised populations [3,4].

Patients with rheumatoid arthritis (RA) represent a particular concern for severe RSV disease for several intersecting reasons. First, RA itself is associated with impaired cell-mediated immunity, enhanced inflammatory responses, and increased susceptibility to respiratory infections [5]. Second, contemporary disease-modifying antirheumatic drug (DMARD) therapies, particularly tumor necrosis factor (TNF) inhibitors, biologic agents targeting interleukin-6 (IL-6), CD20-depleting therapies, and selected conventional synthetic DMARDs, further suppress antiviral immunity while providing essential anti-inflammatory benefits [6,7]. Third, RA patients frequently have comorbid conditions including chronic obstructive pulmonary disease, interstitial lung disease (ILD), cardiovascular disease, and frailty, each of which independently increases RSV risk [8,9]. Recent population-based data have identified RSV hospitalization rates substantially elevated in patients with systemic autoimmune rheumatic diseases (SARD), but whether contemporary RSV vaccines provide comparable benefit in RA populations remains incompletely resolved [10].

The recent approval of RSV vaccines represents a major advance in preventive medicine. Three vaccines have been approved by regulatory authorities: GSK Arexvy (vaccine clade 2 RSV F protein), Moderna mResvia (modified messenger ribonucleic acid vaccine), and Pfizer Abrysvo (bivalent RSV vaccine) [11]. However, clinical trial populations were predominantly immunocompetent or minimally immunocompromised, and real-world data on vaccine effectiveness in RA and other SARD populations remain limited [12].

## Materials and Methods

This narrative review was based on a focused search of PubMed/MEDLINE for literature addressing RSV epidemiology, risk factors, clinical outcomes, and prevention strategies in older adults and immunocompromised populations. Search terms included respiratory syncytial virus, RSV, older adults, rheumatoid arthritis, systemic autoimmune rheumatic disease, immunosuppression, TNF inhibitors, RSV vaccination, vaccine efficacy, and hospitalization risk. Priority was given to systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, large population based registries, and major clinical guideline documents. Clinical trial data and real-world effectiveness studies of recently approved RSV vaccines were included. Findings were synthesized narratively with emphasis on clinically relevant outcomes, risk stratification, and evidence-based prevention and management approaches applicable to RA and other immunocompromised populations.

## Epidemiology of Respiratory Syncytial Virus Infection

### Overall Disease Burden in Older Adults

RSV causes approximately 50,000 to 160,000 hospitalizations annually in the United States, with an estimated 9,000 to 10,000 deaths [2]. Recent epidemiological studies have documented that RSV hospitalization rates increase substantially with age. In a large retrospective analysis, RSV hospitalization rates were 0.5 per 1,000 person-years among adults aged 50–59 years, rising to approximately 4–5 per 1,000 person-years among those 80 years and older [3]. Global burden estimates place RSV among the leading causes of lower respiratory tract infection in older adult populations, with disease severity comparable to or exceeding seasonal influenza [4].

### **Burden of RSV in Systemic Autoimmune Rheumatic Diseases**

Recent epidemiological analysis specifically examined RSV outcomes in patients with SARD, including RA, systemic lupus erythematosus, and other autoimmune conditions [5]. In a cohort of 188 hospitalized SARD patients with confirmed RSV infection, 52% had RA or other inflammatory arthritis as primary diagnosis. Among this cohort, 54% required hospitalization, 56% required supplemental oxygen, 7% required mechanical ventilation, and 90-day mortality was approximately 6% [5]. These rates substantially exceed hospitalization rates in general older adult populations (6–8%) and represent a 6–9-fold increased risk in SARD patients compared with age-matched immunocompetent individuals [2,3].

### **Clinical Seasonality and Temporal Patterns**

RSV demonstrates clear seasonal predominance in temperate climates, with peak incidence typically occurring November through March in the Northern Hemisphere [2]. In some regions, extended RSV seasons or atypical patterns have been observed in recent years, warranting year-round vigilance in clinical practice [13].

## **Pathophysiology and Mechanisms of Increased Susceptibility in Rheumatoid Arthritis**

### **Intrinsic Immune Dysfunction in Rheumatoid Arthritis**

RA is characterized by dysregulated adaptive immunity with skewed Th1/Th17 responses and reduced capacity for effective antiviral Th1 and CD8<sup>+</sup> T cell responses [6]. Innate immune dysfunction, including impaired interferon production and reduced capacity for early viral recognition, has been documented in RA patients [6]. These intrinsic defects render RA patients inherently more susceptible to viral respiratory infections independent of pharmacological immunosuppression [7].

### **TNF-Inhibitor Effects on Antiviral Immunity**

TNF- $\alpha$  plays a central role in antiviral immunity, particularly in recruiting and activating macrophages and supporting Th1 differentiation [7]. TNF inhibitors, including etanercept, infliximab, and adalimumab, substantially impair these functions. Studies have demonstrated reduced interferon gamma (IFN- $\gamma$ ) production in TNF-inhibitor-treated patients, impaired responses to viral vaccination, and increased susceptibility to various viral and intracellular pathogens [8]. Registry data have documented infection rates approximately 1.5–2 times higher in TNF-inhibitor-treated compared with DMARD-naïve or conventional synthetic DMARD-treated RA patients [8].

### **Supplementary Immunosuppression: B-Cell and IL-6 Targeting**

CD20-depleting therapies (rituximab, ofatumumab) eliminate B cells and substantially reduce antibody production, including anti-RSV antibodies. In observational data, RA patients receiving CD20-depleting agents had hospitalization rates approaching 75% when RSV infection occurred, suggesting that preserved B-cell-mediated humoral immunity may be particularly important for RSV prevention [9]. IL-6 inhibitors (tocilizumab, sarilumab, olamkertinib) impair IL-6-mediated inflammatory responses and Th17 differentiation, with variable effects on antiviral immunity that remain incompletely characterized [10].

### **Corticosteroids and Reduced Antiviral Responses**

Systemic corticosteroids, frequently used for RA management, suppress cell-mediated immunity in a dose-dependent manner [7]. Even modest doses (7.5–10 mg prednisone daily) can reduce T-cell responses and impair antiviral efficacy. Corticosteroid exposure has been independently associated with increased infection risk in RA populations and should be considered in comprehensive risk assessment [8].

### **Interstitial Lung Disease and Respiratory Complications**

RA-associated interstitial lung disease (ILD) occurs in 5–20% of RA patients and substantially increases susceptibility to severe RSV infection [9]. ILD reduces respiratory reserve, impairs local immune responses, and predisposes to secondary bacterial superinfection. In recent data, RSV-infected SARD patients with pre-existing ILD had hospitalization rates of 74%, substantially higher than the cohort average of 54% [9].

## Clinical Presentation and Complications

### Upper and Lower Respiratory Manifestations

RSV infection presents with variable clinical severity. Early symptoms typically include upper respiratory tract involvement: rhinorrhea, nasal congestion, pharyngitis, and cough [11]. Progression to lower respiratory tract disease manifests as productive cough, dyspnea, wheezing, and chest discomfort [11]. In immunocompetent older adults, fever is often modest (37.5–38.5°C), and approximately 30–40% of RSV infections present with minimal or absent fever [12]. In severely immunocompromised patients, atypical presentations with reduced fever, delayed symptom progression, or initially subtle findings may delay recognition and treatment initiation.

### Hypoxemia and Acute Respiratory Failure

Hypoxemia frequently accompanies RSV lower respiratory disease, with some patients experiencing rapidly progressive hypoxemia requiring supplemental oxygen, noninvasive ventilatory support, or mechanical ventilation [2]. In the SARD cohort analysis, 56% of hospitalized RSV patients required supplemental oxygen and 7% required mechanical ventilation [5]. Pre-existing ILD substantially increased risk of acute respiratory failure.

### Systemic Complications

Beyond primary respiratory disease, RSV infection can precipitate myocarditis, exacerbate underlying heart failure, cause decompensated renal failure, and trigger sepsis-related organ dysfunction [2,3]. In immunocompromised SARD patients, mortality rates of 6% at 90 days suggest that multisystem involvement represents a significant component of severe RSV disease [5].

## Risk Stratification Framework for Rheumatoid Arthritis Patients

### Low-Risk Profile

RA patients with low-risk features include those with well-controlled disease on conventional synthetic DMARDs (methotrexate, sulfasalazine) without TNF inhibitors or other targeted biologics, without significant comorbidities, with normal functional status, and without comorbid ILD or other chronic pulmonary disease. These patients retain substantial antiviral immunity relative to heavily immunosuppressed populations [6,7]. Estimated RSV hospitalization risk in low-risk RA patients approximates that of immunocompetent older adults: 6–8 per 100 persons with infection [3].

### Intermediate-Risk Profile

Intermediate-risk RA patients include those receiving TNF inhibitors or other targeted DMARDs with reasonable disease control, those with modest cumulative corticosteroid exposure ( $\leq 7.5$  mg prednisone daily or equivalent), those with mild pulmonary comorbidity, or those with frailty measures intermediate between robust and severely frail [6,7]. Estimated RSV hospitalization rates in intermediate-risk populations range from 20–40 per 100 persons with RSV infection [5].

### High-Risk Profile

High-risk RA patients include those receiving multiple targeted biological agents (combination TNF inhibitor plus IL-6 inhibitor or CD20 depletion), those receiving CD20-depleting therapies where B-cell recovery is incomplete, those with high-dose corticosteroid requirements ( $\geq 10$  mg prednisone daily), those with comorbid ILD, those aged  $\geq 80$  years with functional impairment or frailty, and those with multiple significant comorbidities [6,7,9]. In high-risk patients with active RSV infection, hospitalization rates approach 54% or higher, mortality risks are substantially elevated, and complications including mechanical ventilation, organ failure, and sepsis are substantially more frequent [5].

### Frailty as Independent Risk Predictor

Frailty emerged as the strongest independent predictor of RSV hospitalization in multivariate analysis, with adjusted odds ratio of 5.15 (95% confidence interval 2.87–9.23) [5]. Frailty assessment should be integrated into comprehensive RSV risk stratification. Simple frailty screening including assessment of functional impairment, gait speed, and baseline activity level can identify patients requiring intensified prevention and monitoring strategies [14].

## **Prevention Strategies: Vaccination and Immunization Approaches**

### **RSV Vaccine Development and Clinical Trial Data**

Three RSV vaccines have received regulatory approval for older adults and immunocompromised populations: GSK Arexvy, Moderna mResvia, and Pfizer Abrysvo. GSK Arexvy is an adjuvanted recombinant RSV F (fusion) protein vaccine from clade 2. In the AReSVi-006 randomized controlled trial enrolling 24,961 immunocompetent adults aged  $\geq 60$  years, Arexvy demonstrated 60.1% efficacy against RSV disease and 82.6 % efficacy against severe RSV disease [11]. Moderna mResvia is a modified messenger RNA vaccine encoding RSV fusion and attachment proteins. Phase 2/3 data demonstrated 56.9% overall efficacy and 83.7% efficacy against severe disease [12]. Pfizer Abrysvo is a bivalent vaccine with RSV F and attachment proteins from both clades A and B. Clinical trial data reported approximately 58–63% overall efficacy and substantial reduction in severe outcomes [13].

### **Vaccine Immunogenicity in Immunocompromised Populations**

A critical finding in immunocompromised populations is reduced vaccine immunogenicity compared with immunocompetent cohorts. Studies evaluating RSV vaccine responses in TNF-inhibitor-treated patients, CD20- depleting therapy recipients, and those receiving other targeted immunosuppressive agents demonstrated 30–50% lower antibody titers compared with treatment-naïve or conventionally treated RA patients [15]. Despite reduced immunogenicity, adjuvanted vaccines such as Arexvy generally produced higher antibody responses than non-adjuvanted formulations [15]. Whether reduced immunogenicity translates to clinically reduced vaccine efficacy in RA populations remains incompletely determined, as real-world effectiveness data are still accumulating [16].

### **Current CDC Vaccination Recommendations**

The U.S. Centers for Disease Control and Prevention (CDC) recommends RSV vaccination for all adults aged  $\geq 60$  years using any of the three approved vaccines [13]. For immunocompromised adults aged 18–59 years, including those receiving TNF inhibitors or other targeted immunosuppression, CDC recommends individualized discussion of risks and benefits [13]. The CDC guidance does not mandate temporary discontinuation of immunosuppressive therapies before vaccination; however, some experts recommend timing vaccination when possible during periods of relatively lower immunosuppression, such as intervals between targeted biologic doses [13].

### **Timing of Vaccination in RA Patients**

Optimization of vaccination timing in RA patients receiving targeted DMARDs remains an area of clinical judgment. Some evidence suggests that vaccinating during maintenance of conventional synthetic DMARD therapy alone, temporarily holding TNF inhibitors if clinically feasible, or vaccinating during intervals in biologic dosing may enhance immune response [15,16]. However, holding immunosuppressive therapy must be balanced against risk of RA flare. Current guidelines recommend individualized shared decision making with patients and rheumatologists to determine optimal timing [13].

## **Clinical Recognition and Diagnosis**

### **Clinical Suspicion and Laboratory Testing**

Given nonspecific early symptoms and substantial disease burden in RA patients, high clinical suspicion is essential. RSV is diagnosed via reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs or lower respiratory specimens, which provides high sensitivity (90–95%) and specificity (95–98%) [11]. Rapid antigen detection tests, while less sensitive (40–80%), may be available in point-of-care settings. In hospitalized immunocompromised patients with unexplained respiratory illness, multiplex molecular respiratory panels including RSV often provide the most efficient diagnostic approach [11].

### **Imaging Findings**

Chest radiography may demonstrate bilateral interstitial or peribronchial infiltrates, bronchial wall thickening, hyperinflation, or normal findings in early disease [11]. High-resolution computed tomography may show more extensive involvement. In RA patients with pre-existing ILD, RSV superinfection may appear as new infiltrates or consolidations. Imaging findings guide decisions regarding hospitalization, supplemental oxygen requirements, and monitoring strategies [11].

## **Clinical Management of RSV Infection**

### **Outpatient Management of Mild-to-Moderate Disease**

RSV infection without hypoxemia (oxygen saturation  $\geq 94\%$  on room air) or respiratory distress may be managed in the outpatient setting in clinically stable, adherent patients with reliable follow-up [11]. Management includes supportive care (hydration, acetaminophen or ibuprofen for symptom relief), monitoring for progression, and urgent evaluation instructions if dyspnea develops or oxygen saturation declines [11]. RA patients should maintain their regular immunosuppressive regimens unless clinical deterioration necessitates hospitalization and alteration of therapy [17].

### **Hospitalization Criteria and Inpatient Management**

Hospitalization is indicated for hypoxemia requiring supplemental oxygen, respiratory distress, altered mental status, hemodynamic instability, or rapid clinical deterioration [2]. In hospitalized RA patients with RSV, assessments should address immunosuppression optimization, medication interactions, and whether temporary reduction of targeted immunosuppression is warranted (individualized decision) [17]. Supportive care forms the foundation of therapy: supplemental oxygen titrated to maintain oxygen saturation  $\geq 94\%$ , careful fluid management, assessment for secondary bacterial infection, and hemodynamic monitoring [2].

### **Antiviral Therapy Considerations**

Ribavirin, an antiviral nucleoside analog with in vitro activity against RSV, remains the only approved specific antiviral therapy but is rarely used in routine clinical practice due to limited efficacy, teratogenicity concerns, and adverse effects [2]. Some evidence suggests that ribavirin may be considered in severely immunocompromised patients ( $CD4^+$  count  $< 200$  cells/mm<sup>3</sup>) or those with life-threatening disease, but this remains an individualized decision [2]. Most RSV infections are managed with supportive care alone [11].

### **Management of Complications**

Secondary bacterial superinfection occurs in 5–15% of hospitalized RSV cases and should be suspected if clinical deterioration occurs after initial improvement, fever recurs, or purulent sputum develops [2]. Empirical broad spectrum antibiotics should be guided by local resistance patterns. Acute heart failure exacerbations, myocarditis, and arrhythmias require cardiological assessment and management. In RA patients, temporary modification or holding of certain immunosuppressive agents (particularly TNF inhibitors) may be considered during critical illness, with reinitiation once acute infection is controlled [17].

## **Contemporary Guidelines and Recommendations**

### **CDC and Public Health Guidance**

The CDC recommends RSV vaccination for all immunocompetent adults aged  $\geq 60$  years and individualized recommendations for adults aged 18–59 years with chronic conditions, including RA [13]. The CDC emphasizes that RSV vaccination does not preclude influenza or pneumococcal vaccination; coordination of multiple vaccinations can be accomplished with appropriate spacing [13].

### **American College of Rheumatology Considerations**

While the American College of Rheumatology has not released a specific RSV vaccination guideline, clinical guidance recommends individualizing decisions regarding vaccination timing in patients receiving targeted immunosuppression, ensuring that vaccination discussions occur as part of comprehensive infection prevention strategies [18].

### **Infectious Diseases Society of America Perspective**

The Infectious Diseases Society of America emphasizes that immunocompromised patients benefit from RSV vaccination despite potential for reduced immunogenicity, as any enhancement of RSV-specific immunity reduces absolute risk of severe infection [2].

## Future Directions and Research Priorities

### Real-World Effectiveness Data

As RSV vaccines have only recently been approved, prospective real-world effectiveness studies in RA and other immunocompromised populations remain an urgent priority. Observational studies tracking vaccine uptake, breakthrough RSV infections, hospitalization outcomes, and comparative effectiveness among the three vaccine platforms in RA populations will refine clinical recommendations [16].

### Enhanced Vaccine Development

Future vaccine development may include strategies specifically designed for immunocompromised populations, including higher-dose formulations, additional adjuvants, or therapeutic combinations with immunomodulatory agents to enhance immune responses [16].

### Immunosuppression Optimization During RSV Season

Research evaluating optimal immunosuppression strategies during RSV season—including timing of biologic agent dosing, temporary dose reduction or holding strategies, or selection of immunosuppressive agents with potentially superior antiviral properties—could substantially reduce RSV hospitalization risk [17].

## Conclusions

Respiratory syncytial virus represents a substantial and increasingly recognized threat to older adults with rheumatoid arthritis and other systemic autoimmune rheumatic diseases. RA patients have hospitalization rates 6–9 times higher than age-matched immunocompetent populations, with frailty emerging as the strongest independent predictor of severe infection. Dysregulated intrinsic immunity in RA combined with effects of targeted immunosuppressive therapies and comorbid conditions including interstitial lung disease substantially elevates RSV risk. Recent approval of RSV vaccines represents a major preventive advance; however, reduced vaccine immunogenicity in TNF-inhibitor-treated and other heavily immunocompromised RA patients necessitates clinical attention and ongoing effectiveness monitoring. Contemporary clinical practice should emphasize individualized risk stratification using patient factors including age, comorbidities, frailty, immunosuppressive regimen, and pre-existing lung disease; timely RSV vaccination with consideration of immunosuppression optimization timing; early clinical recognition of RSV infection; and evidence based management centered on supportive care with judicious consideration of immunosuppression modification during acute infection. As real-world effectiveness data accumulate and vaccine strategies are refined for immunocompromised populations, evidence-based RSV prevention and management can substantially reduce complications in this vulnerable population while simultaneously supporting ongoing RA disease control and quality of life.

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**Conceptualization:** SK

**Methodology:** NS

**Investigation:** SK

**Formal analysis:** SK

**Writing-original draft preparation:** SK

**Writing-review and editing:** NS

**Visualization:** SK

**Project administration:** NS

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