

# Rates of infections in children and adolescents with rheumatic diseases: analysis of German nationwide health insurance data

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## Introduction

Infections might be more frequent in children and adolescents with inflammatory rheumatic diseases compared to the general population due to disease-inherent immune dysregulation and/or required medication. Studies upon this topic are scarce and show conflicting results.

## Objective

Compare rates of selected infections, hospitalization because of infection and antibiotic therapies among children and adolescents with different rheumatic diseases and matched controls using nationwide health insurance data.

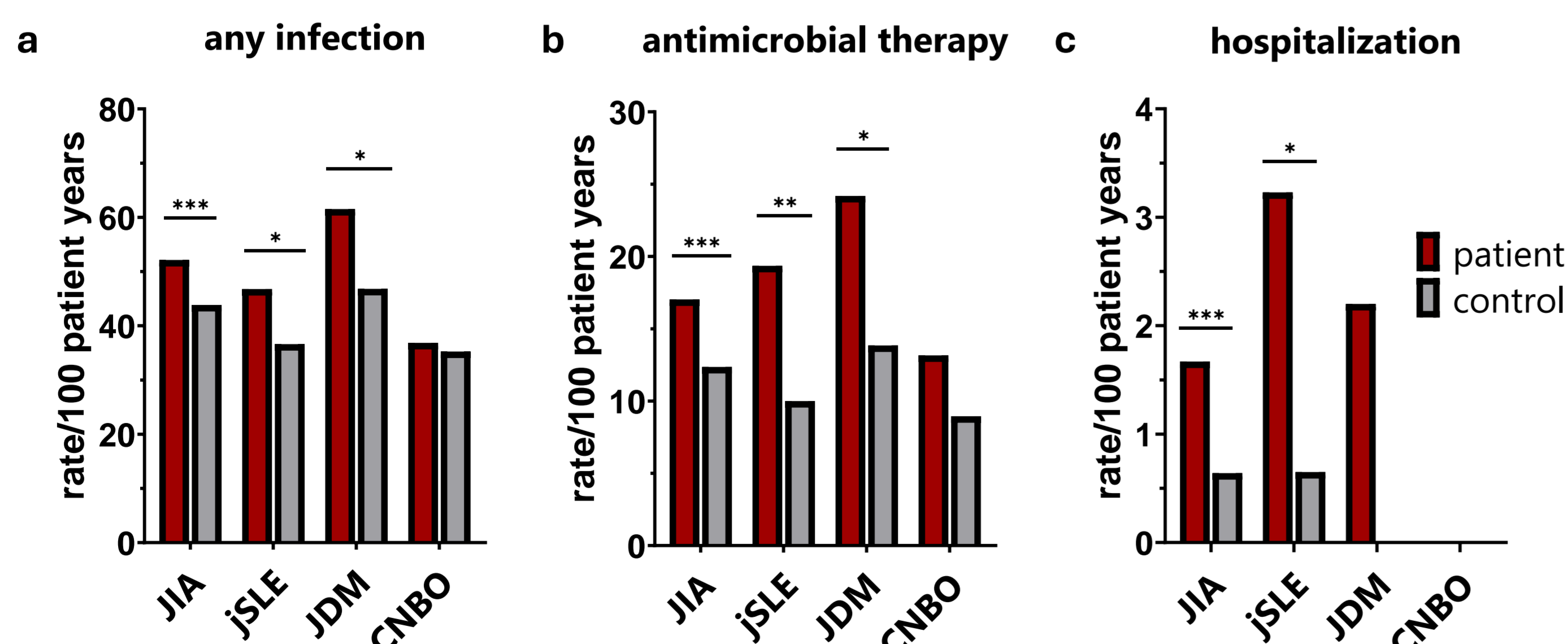
## Methods

Nationwide data from the statutory BARMER health insurance company for 2018-2023 were analyzed. The study included individuals aged 0-18 years with an ICD-10-GM diagnosis of juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (jSLE), juvenile dermatomyositis (jDM) or chronic non-bacterial osteomyelitis (CNBO) in at least two quarters. Rates of selected infections, identified by ICD-10-GM codes (all infectious and parasitic diseases, 41 individual infections), hospitalization for infection, and annual antibiotic prescription rates (identified by Anatomical Therapeutic Chemical [ATC] code) were assessed and compared to sex- and age-matched controls. Incidence rates of infections, antimicrobial therapies and hospitalizations were calculated. Poisson regression models were used in order to assess the association of infections with rheumatic diseases as well as treatments.

## Results

|                             | JIA         | jSLE        | jDM         | CNBO        |
|-----------------------------|-------------|-------------|-------------|-------------|
| patient years)              | 7796        | 124         | 91          | 38          |
| control years)              | 38912       | 620         | 455         | 190         |
| age, years, (mean [SD])     | 11,8 (4,03) | 14,7 (2,42) | 10,4 (4,66) | 13,5 (3,07) |
| female sex (%)              | 66,3        | 84,7        | 70,3        | 50          |
| therapy of patients (%):    |             |             |             |             |
| csDMARDs                    | 32,2        | 63,7        | 60,4        | 18,4        |
| MTX                         | 28,8        | 1,6         | 35,2        | 18,4        |
| hydroxychloroquine          | 0,4         | 50,0        | 13,2        | 0,0         |
| MMF                         | 0,1         | 8,1         | 5,5         | 0,0         |
| bDMARDs                     | 23,0        | 4,0         | 0,0         | 13,2        |
| Etanercept                  | 8,9         | 0,0         | 0,0         | 7,9         |
| Adalimu-/golimu-/infliximab | 10,8        | 0,8         | 0,0         | 5,3         |
| tsDMARDs                    | 0,1         | 2,4         | 0,0         | 0,0         |
| Glucocorticoids (GC)        | 10,8        | 50,0        | 30,8        | 7,9         |

**Table 1: Demographic and clinical characteristics of patients with rheumatic diseases and controls, during years 2018-2023.** Each patient was matched with 5 controls of same age and sex.



**Figure 1: Estimated rates of any infection, antimicrobial therapy and infection-related hospitalization/100 patient years.** In patients with JIA, jSLE and JDM all three items were encoded more often than in respective controls. Also, prescriptions of antimicrobials and hospitalizations due to infection were more common and were particularly high in patients with SLE and JDM. Mean rates were estimated over all patients/controls and years. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001.

|                    | JIA         |             |                | jSLE        |             |                |
|--------------------|-------------|-------------|----------------|-------------|-------------|----------------|
|                    | rate/100 py | RR (95% CI) |                | rate/100 py | RR (95% CI) |                |
|                    | control     | patients    |                | control     | patients    |                |
| acute sinusitis    | 1,6         | 2,2         | 1,4 (1,2-1,7)  | 2,1         | 6,5         | 3,3 (1,3-8,1)  |
| acute bronchitis   | 5,6         | 7,0         | 1,3 (1,2-1,4)  | 2,3         | 4,0         | 1,8 (0,6-5,2)  |
| bact. pneumonia    | 0,6         | 0,7         | 1,2 (0,9-1,7)  | 0,3         | 0,8         | 2,6 (0,2-30,0) |
| bact. meningitis   | 0,0         | 0,0         | 1,0 (0,1-8,6)  | 0,0         | 0,0         | -              |
| bact. enteritis    | 0,1         | 0,3         | 2,1 (1,3-3,6)  | 0,3         | 0,8         | 2,5 (0,2-28,1) |
| pyelonephritis     | 0,1         | 0,2         | 3,1 (1,7-5,7)  | 0,2         | 0,8         | 5,0 (0,3-81,4) |
| covid-19           | 4,5         | 4,7         | 1,1 (1,0-1,2)  | 6,0         | 6,5         | 1,1 (0,5-2,5)  |
| influenza          | 0,2         | 0,2         | 1,3 (0,8-2,3)  | 0,2         | 0,8         | 5,2 (0,3-87,4) |
| herpesviral inf.   | 0,8         | 1,3         | 1,6 (1,3-2,0)  | 0,6         | 1,6         | 2,5 (0,5-14,0) |
| herpes zoster      | 0,1         | 0,3         | 3,4 (2,1-5,5)  | 0,5         | 0,8         | 1,7 (0,2-16,3) |
| candidiasis        | 0,8         | 1,2         | 1,6 (1,2-2,0)  | 1,1         | 1,6         | 1,4 (0,3-7,0)  |
| mycobacterial inf. | 0,0         | 0,0         | -              | 0,0         | 1,6         | -              |
| toxoplasmosis      | 0,0         | 0,0         | -              | 0,0         | 0,8         | -              |
| tuberculosis       | 0,0         | 0,1         | 5,0 (1,6-15,5) | 0,0         | 0,0         | -              |

**Table 2 Estimated rates of specific infections/100 patient years (py) and relative risk (RR) in patients with JIA and patients with jSLE compared to matched controls.** Overall, 41 different infections were screened. Several viral and bacterial infections including opportunistic infections are increased in patients with rheumatic diseases. Significance is limited in patients with jSLE, JDM (not shown) and CNBO (not shown) due to low case numbers. Mean rates were estimated over all patients/controls and years.

| therapy                 | no DMARD/GC        | GC <sup>1</sup>    | csDMARD <sup>2</sup>   | bDMARD <sup>2</sup> | cs+bDMARD <sup>2</sup> |
|-------------------------|--------------------|--------------------|------------------------|---------------------|------------------------|
| reference               | control            | no GC <sup>1</sup> | no DMARDs <sup>2</sup> |                     |                        |
| any infection           | 1,2<br>(1.1 - 1.3) | 2,0<br>(1.7 - 2.3) | 1,2<br>(1.1 - 1.3)     | 1,0<br>(0.9 - 1.2)  | 1,4<br>(1.2 - 1.6)     |
| hospitalization         | 2,5<br>(1.9 - 3.3) | 2,4<br>(1.6 - 3.8) | 0,6<br>(0.4 - 1.0)     | 1,1<br>(0.6 - 1.9)  | 0,9<br>(0.6 - 1.6)     |
| antimicrobial treatment | 1,2<br>(1.1 - 1.3) | 1,5<br>(1.2 - 1.7) | 1,2<br>(1.0 - 1.4)     | 1,5<br>(1.2 - 1.7)  | 1,6<br>(1.4 - 1.9)     |
| acute bronchitis        | 1,1<br>(1.0 - 1.2) | 2,1<br>(1.7 - 2.7) | 1,2<br>(1.0 - 1.5)     | 0,7<br>(0.5 - 0.9)  | 1,1<br>(0.8 - 1.4)     |
| bact. pneumonia         | 1,0<br>(0.7 - 1.6) | 2,7<br>(1.5 - 5.2) | 0,9<br>(0.5 - 1.8)     | 0,8<br>(0.4 - 2.0)  | 0,9<br>(0.4 - 2.1)     |
| Pyelonephritis          | 3,2<br>(1.5 - 6.9) | 1,1<br>(0.2 - 5.2) | 1,2<br>(0.4 - 3.9)     | 0,6<br>(0.1 - 4.7)  | 1,1<br>(0.2 - 5.1)     |
| Covid-19                | 1,0<br>(0.8 - 1.2) | 1,2<br>(0.9 - 1.7) | 1,1<br>(0.9 - 1.5)     | 1,0<br>(0.7 - 1.4)  | 1,2<br>(0.9 - 1.7)     |
| Influenza               | 1,4<br>(0.7 - 2.7) | 3,3<br>(1.1 - 9.9) | 0,4<br>(0.1 - 1.8)     | 0,4<br>(0.1 - 3.4)  | 1,3<br>(0.4 - 4.3)     |
| herpesviral inf.        | 1,1<br>(0.8 - 1.5) | 2,3<br>(1.5 - 3.7) | 2,1<br>(1.3 - 3.5)     | 1,4<br>(0.7 - 2.7)  | 2,5<br>(1.4 - 4.3)     |
| herpes zoster           | 1,9<br>(0.9 - 4.0) | 1,6<br>(0.6 - 4.2) | 1,1<br>(0.4 - 3.8)     | 2,2<br>(0.7 - 7.1)  | 4,9<br>(1.9 - 12.4)    |
| Candidiasis             | 1,4<br>(1.0 - 1.9) | 1,6<br>(0.9 - 2.9) | 0,9<br>(0.5 - 1.5)     | 1,0<br>(0.5 - 1.9)  | 1,4<br>(0.8 - 2.5)     |

**Table 3: Adjusted relative risk of JIA patients with no/different antirheumatic therapies in comparison to a reference group.** Even without GC or DMARD therapy, overall infections, antimicrobial therapies and infection-related hospitalization were more common in JIA patients compared to controls. Especially GC treatment increased the risk for infections further.

<sup>1</sup>Adjusted for year and DMARD therapy or <sup>2</sup>year and GC therapy.

## Conclusion

Patients with JIA, jSLE and JDM seek medical attention for infections more frequently, are more often hospitalized and receive more antibiotics than age-matched controls. In JIA, this was the case even for patients without GC or DMARDs, however, rates of hospitalized infections were overall low. Particularly GC treatment increases the risk for several infections including antimicrobial treatment and hospitalization significantly.