**Title**

Burden of infections in early life associates with later risk of infections and systemic antibiotic episodes in childhood

**Authors**

Nicklas Brustad, MD, PhD1, Frederik Buchvald, MD, PhD2; Signe Kjeldgaard Jensen, MD, PhD1; Julie Nyholm Kyvsgaard, MD, PhD1; Nilo Vahman, MD, PhD1; Jonathan Thorsen, MD, PhD1; Ann-Marie Malby Schoos, MD, PhD, DMSc1,3,4; Ulrikka Nygaard, MD, PhD2,4; Nadja Vissing, MD, PhD2; Jakob Stokholm, MD, PhD1,3,4; Klaus Bønnelykke MD, PhD1,5; Bo Chawes, MD, PhD, DMSc1,5

**Affiliation:**

1. COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Denmark
2. Department of Pediatrics, Rigshospitalet, Denmark
3. Department of Pediatrics, Slagelse Hospital, Denmark
4. Department of Food Science, University of Copenhagen, Frederiksberg C, Denmark
5. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

**Correspondence:**

Nicklas Brustad, MD, PhD

Ledreborg Allé 34, 2820, Gentofte, Denmark

E-mail: nicklas.brustad@dbac.dk, telephone: +45 2892 4131

**ABSTRACT (340 words)**

**Importance:** A high infection burden in early childhood is common and a risk factor for later disease development. However, longitudinal birth cohort studies investigating early life infection burden and later risk of infections and antibiotic episodes are lacking.

**Objective:** To investigate whether early-life infection burden associated with later risk of infection and systemic antibiotic treatment episodes.

**Design, setting and participants:** A longitudinal cohort study of 700 children from the Danish population based COPSAC2010 birth cohort with inclusion between November 2008 to November 2010.

**Exposures:** Daily diary registered common infection episodes of cold, acute otitis media, tonsillitis, pneumonia, gastroenteritis and fever episodes from birth until age 3 years.

**Main outcome and measurements:** After age 3 years, the children were followed with longitudinal monitoring of moderate-severe infection diagnoses and systemic antibiotic prescriptions from national databases until February 1, 2024, where they had completed the age 10- or 13-year visit. Incidence rate ratios (IRRs) were calculated from Quasi-Poisson regressions. Children with immune deficiencies or congenital diseases were excluded. All analyses were adjusted for social and environmental confounders.

**Results:** A total of 614 children with diary data age 0-3 years had complete follow-up until age 10-13 years and there were no differences in baseline characteristics between the children having vs not having available diary data. Children with high vs low burden of diary-registered infections age 0-3 years, i.e., above vs. below the median of 16 had increased risks of later moderate-severe infections (181 vs 87 episodes), adjusted IRR (95% CI): 2.39 (1.52-3.89), p<0.001 and systemic antibiotic episodes (799 vs 623 episodes): 1.34 (1.07-1.68), p=0.01 until age 10-13 years. Each diary infection episode also increased later risk of moderate-severe infections: 1.05 (1.02-1.08) p<0.001 and systemic antibiotic episodes; 1.02 (1.01-1.04) p<0.001. Subtype analyses demonstrated significant associations between each cold, acute otitis media, pneumonia, gastroenteritis and fever episode age 0-3 years and risk of later moderate-severe infections or systemic antibiotic episodes.

**Conclusions and relevance:** This longitudinal cohort study from birth until age 10-13 years suggests that early life infection burden continues throughout childhood and associates with later antibiotic treatments independent of social and environmental risk factors. These findings are important for prognosis and follow-up of children experiencing a high burden of common infections in early life.