////Title: The Frequency and Impact of *Chlamydia Pneumoniae* Infection in Chronic Asthma Patients

////Stand-first:

Chlamydia [Kla-MID-ee-yuh] *pneumoniae* [new-MOHN-ee-eye] (or Cp for short) is a respiratory bacterium that causes treatable lung infections in humans and has been linked to the development of asthma. In a recent study, Dr David L. Hahn [H-aa-n] at St Mary's Hospital in Madison, Wisconsin, USA, conducted a systematic review and meta-analysis of the available published data on the frequency and impact of Cp infection in child and adult asthma patients, and considered the potential implications for treatment.

////Body text:

The contribution of *Chlamydia pneumoniae* (Cp) in the development of asthma is readily accepted. However, information on the proportion of asthma cases potentially caused by Cp, also known as the population attributable risk or PAR, has not been reported. Additionally, the link between Cp infection and asthma severity has heretofore not been systematically well documented. Antibodies such as IgG, IgA and IgE are produced in the body in response to infection, are easily detected in blood, and may be used as biomarkers.

Treatment options for the management of severe asthma include the use of antibiotics known as macrolides. Macrolides are commonly used in the treatment of respiratory infections, although their mechanism of action in asthma is currently unknown.

Previous research has identified associations between Cp biomarkers and chronic asthma, although there is a distinct lack of large, long-term, forward-looking studies investigating Cp infection in the population. Furthermore, the most recent review of observational studies assessing Cp biomarkers and chronic asthma in children and adults was published in 2005.

With this in mind, and with the recent inclusion of macrolides as a recognised treatment for severe asthma in respiratory and thoracic society guidelines, Dr David L. Hahn at St Mary's Hospital in Madison, Wisconsin, USA, recently conducted an up-to-date systematic review and meta-analysis of the published literature.

He aimed to establish what proportion of chronic stable asthma is potentially attributable to or influenced by chronic Cp infection, or whether selected Cp infection biomarkers are more frequent in individuals diagnosed with chronic stable asthma in comparison to individuals without asthma. Furthermore, the potential for identifying the possible mechanisms of action of macrolides to assist clinicians in the treatment of severe asthma was considered.

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Dr Hahn searched for relevant articles published between the years 2000 and 2020. Studies were included in the review if one or more Cp biomarkers were reported, the population studied were diagnosed with chronic asthma by a clinician, a non-asthmatic control group was used, and sufficient information was presented to calculate biomarker frequency in the asthmatic group and control group separately. Additionally, prospective studies were included only if there was a follow-up duration of at least five years. Ultimately, twenty publications were included and study quality was assessed using a risk of bias tool.

Appropriate data for the meta-analysis were available from 25 studies, including those cited in the 2005 review. The Cp biomarkers chosen for meta-analysis were IgG, IgA, and IgE in peripheral blood. Cp IgG and IgA were analysed separately for children and adults but IgE was analysed for both age

groups combined due to the small number of available studies. Additionally, a meta-analysis combining biomarkers and age groups was performed to estimate and compare the PARs for asthma severity subgroups. Severity was classified as mild/controlled, moderate/partly controlled, and severe/uncontrolled.

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For the updated systematic review, ten studies involving children from seven different countries were included. Five of the studies reported one or more positive associations of biomarkers with asthma. Ten studies involving adults from eight different countries were also included. Again, five of the studies reported one or more positive associations of biomarkers with asthma. It was noted that there were no long-term prospective studies designed specifically to investigate Cp infection in asthma.

Dr Hahn's comprehensive meta-analysis included eleven studies from the 2005 review, plus fourteen studies published between 2005 and 2020. The meta-analysis revealed no significant associations between Cp IgG or IgA and asthma in children, an unsurprising finding given that an antibody response to Cp infection in children is often undetectable. Conversely, Cp IgG and IgA were associated with a modest but significant PAR in adults, which may be attributable to the fact that the background prevalence of Cp antibody in the adult population is high.

Of most interest, Cp IgE was associated with a large, significant PAR in children and adults combined. When analysis of Cp biomarkers was conducted with regards to asthma severity in children and adults combined, a strongly positive, highly significant association with all three biomarkers was identified. Furthermore, the PAR increased markedly in relation to the degree of severity.

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Dr Hahn's update on observational studies has, for the first time, provided an estimation of the PAR of Cp biomarkers in chronic asthma. This review and meta-analysis focussed on chronic asthma, not least because studies about the long-term management of chronic asthma using macrolides have proven to be clinically beneficial. The underlying mechanism of action of macrolides in the treatment of chronic asthma remains elusive but may involve anti-inflammatory as well as antimicrobial effects.

Whilst IgG antibodies are suggestive of past infection, IgA antibodies may indicate an ongoing chronic infection. IgE antibodies are produced in response to an allergen, and asthma is almost always associated with an IgE-related reaction. It is therefore possible that Cp expresses an antigen that is responsible for generating an IgE response in asthmatics.

The minimal association between Cp IgG and IgA antibodies and asthma observed in children and adults suggest that these biomarkers may not be clinically reliable in predicting which patients will benefit from macrolide treatment. However, the fact that Cp IgE PAR stands at almost 50% suggests that Cp chronic infection may be a significant contributor to moderate and severe childhood and adult asthma.

Indeed, current methods for the prevention and treatment of asthma symptoms rely on the avoidance or removal of the antigen in question. Cp IgE may prove to be a valuable predictor of treatable chronic Cp infection in asthma.

In this work, Dr Hahn selected PAR as a measure in the analysis of the data since it provides an outcome that can be easily clinically interpreted. In light of the findings, Dr Hahn suggests that a subset of severely asthmatic patients with Cp infection may particularly benefit from macrolide treatment. Furthermore, he proposes that Cp infection may contribute to at least some cases of less severe asthma.

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Overall, Dr Hahn's systematic review and meta-analysis have provided valuable insight into the frequency of Cp infection in the pathogenesis of asthma. He notes, however, that larger, better designed studies into the potential role of Cp infection in asthma are needed.

In summary, it is recognised that biomarkers of Cp infection are associated with chronic asthma, and PAR is significantly associated with age, severity, and antibody type. The presence of Cp-specific IgE suggests a role for bacterial allergy in moderate and severe asthma. These data may prove useful in guiding research into macrolide mechanisms of action in asthma, and ultimately aid in patient treatment planning while also underscoring important research questions about the role of Cp in asthma.

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This SciPod is a summary of the paper '*Chlamydia pneumoniae* and chronic asthma: Updated systematic review and meta-analysis of population attributable risk', published in the open access journal PLoS ONE. https://doi.org/10.1371/journal/pone.0250034.

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