

Correspondence

Reply

To the Editor:

We thank Professor Hahn¹ for his interest and comments on our article,² which raise several important issues. Clearly childhood asthma is an important clinical problem that may be induced by specific exposures in early life. Webley et al³ have shown that chlamydial lung infections are associated with severe pediatric asthma, and experimental studies indicate that infection may induce sensitization.⁴ Importantly, as Professor Hahn appreciates, we now show that chlamydial infection in early life may promote the development of more severe asthma by permanently modulating the host immune response and altering lung function and structure. Infection alone altered lung structure and reduced lung function in the absence of allergic sensitization and challenge. As we and others have previously highlighted, chlamydial infections are also potentially important in adult-onset asthma, in asthma exacerbations, and in modifying the phenotype of asthma (eg, neutrophilic asthma).^{5,6} Indeed, Wark et al⁷ showed that chlamydial infection is associated with enhanced neutrophilic inflammation in the airways of exacerbating adults with asthma. Significantly, in a forthcoming publication we show that chlamydial infection during allergen sensitization suppresses T_H2 responses and eosinophilic inflammation. However, infection was associated with neutrophilic inflammation and T_H1/T_H17 responses during subsequent allergen exposure in an experimental model of allergic asthma in adult mice.⁸ This study further emphasizes the potential importance of nonallergic mechanisms that may contribute to *Chlamydia*-associated asthma. Collectively, the studies described here show that the specific effects and nature of the association between chlamydial respiratory infection and asthma are likely to be determined by the age of infection and/or the timing of infection relative to allergen exposure. These studies highlight the requirement for research to elucidate the mechanisms that underpin the associations of chlamydial infections and asthma.

Many epidemiologic studies of the link between chlamydial infections and asthma have been performed. The majority used serology,⁵ which have produced contradictory results and led to confusion of the role of *Chlamydia* in asthma. We also agree with Professor Hahn that more detailed longitudinal and prospective epidemiologic studies are required to clarify the role of chlamydial infection. What is needed now is for such studies to be performed using effective, standardized methods for the detection of *Chlamydia*. Such studies would further elucidate the nature of

the association of chlamydial infection and the induction, exacerbation, altered phenotype, and increased severity of asthma in all age groups. Furthermore, more basic studies are required to unravel the mechanisms that underpin these associations. Only after these studies have been conducted will we realize the potential for the identification of effective strategies that prevent and treat infection, which may have beneficial effects for asthma, as well as the sequelae of infection (eg, altered lung structure and reduced lung function).^{5,6}

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Supported by grants from the National Health and Medical Research Foundation of Australia (project grants 401238 and 569219), Asthma Foundation of NSW, the Rebecca Cooper Medical Research Foundation, the University of Newcastle project grants and Brawn Post-Doctoral Fellowship, the Hunter Medical Research Institute, and the Australian Research Council (0559210).

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

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REFERENCES

1. Hahn DL. Chlamydial infection and asthma: is early allergic sensitization the only mechanism? *J Allergy Clin Immunol* 2010; ##:##.
2. Horvat JC, Starkey MR, Kim RY, Phipps S, Gibson PG, Beagley KW, et al. Early-life chlamydial lung infection enhances allergic airways disease through age-dependent differences in immunopathology. *J Allergy Clin Immunol* 2010;125: 617-25.e6.
3. Webley WC, Tilahun Y, Lay K, Patel K, Stuart ES, Andrzejewski C, et al. Occurrence of *Chlamydia trachomatis* and *Chlamydia pneumoniae* in paediatric respiratory infections. *Eur Respir J* 2009;33:360-7.
4. Schröder NW, Crother TR, Naiki Y, Chen S, Wong MH, Yilmaz A, et al. Innate immune responses during respiratory tract infection with a bacterial pathogen induce allergic airway sensitization. *J Allergy Clin Immunol* 2008;122:595-602.e5.
5. Hansbro PM, Beagley KW, Horvat JC, Gibson PG. Role of atypical bacterial infection of the lung in predisposition/protection of asthma. *Pharmacol Ther* 2004;101: 193-210.
6. Korppi M. Management of bacterial infections in children with asthma. *Expert Rev Anti Infect Ther* 2009;7:869-77.
7. Wark PAB, Johnston SL, Simpson JL, Hensley MJ, Gibson PG. *Chlamydia pneumoniae* immunoglobulin A reactivation and airway inflammation in acute asthma. *Eur Respir J* 2002;20:834-40.
8. Horvat JC, Starkey MR, Kim RY, Beagley KW, Preston JA, Gibson PG, et al. Chlamydial respiratory infection during allergen sensitization drives neutrophilic allergic airways disease. *J Immunol* 2010;184:4159-69.

doi:10.1016/j.jaci.2010.03.033