Previous general practitioner consulting behaviour as a predictor of pneumonia in children

To the Editor:

As a consequence of increasing antimicrobial resistance, general practitioners (GPs) are encouraged to prescribe antibiotics only for patients most likely to benefit, for example children at high risk of hospitalisation for pneumonia. Secondary to clinical assessment, knowledge of a child's background may improve the identification of those at high risk, since several studies have described medical, social and environmental risk factors for paediatric community-acquired pneumonia. Most of these studies, including the only two case–control studies conducted in primary care [1, 2], compared cases of pneumonia with healthy community controls, and therefore may have identified risk factors for respiratory tract infections (RTIs) in general and not specifically pneumonia. Two case–control studies used hospital controls with RTIs [3, 4], but these findings may not be applicable to children consulting in primary care. We used an existing case–control study dataset [5] to explore demographic, medical and social risk factors for community-acquired pneumonia or empyema among children consulting in general practice. This is the first such comparison of children seen in primary care with RTIs with and without subsequent hospital presentation for pneumonia.

The selection and recruitment of cases and controls and data collection procedures have been described elsewhere [5]. Cases were recruited from seven hospitals in south Wales, UK. Eligible cases were children aged 6 months to 16 years assessed in hospital and given a clinical or radiographic diagnosis of community-acquired pneumonia or empyema by any treating clinician, with subsequent evidence of 1) pneumonia in the radiologist's report, 2) a principal discharge diagnosis consistent with pneumonia, 3) a history of GP consultation for the index illness before the day of hospital presentation, and 4) registration at a general practice within one of the five local health boards served by the participating hospitals. Controls of similar age who had recently consulted a GP and had been diagnosed with upper RTI, lower RTI or cough, were identified from 65 general practices in the same geographical area. Children with serious underlying medical conditions were excluded.

Carers completed a questionnaire [5] about the index illness and a range of background variables, which they returned by mail. Background variables included demographic data, medical history and social or environmental factors. We also obtained the Welsh Index of Multiple Deprivation (WIMD) 2008 score corresponding to each child's home postcode.

A total of 255 participants were eligible for data analysis, comprising 89 cases (11 empyema and 78 pneumonia) and 166 controls. Our sample size was sufficient to detect an odds ratio of 2.25 or more when comparing cases and controls, with 80% power at the 5% significance level. The flow of participants from recruitment to data analysis, response rates, and comparisons between responders and non-responders have been reported previously, as have the results of bivariate analyses [5].

Background variables with a p-value of less than 0.25 in bivariate analyses qualified for entry into a logistic regression model using a forward stepwise selection procedure (Wald test) with p(entry)=0.20 and p(removal)=0.25. These were: number of GP visits for other illness(es) in the past year (p=0.01), home ownership (p=0.01), firstborn child (p=0.15), living with a daily smoker (p=0.16), sex (p=0.18), lone parent (p=0.21) and WIMD quintile (p=0.21). The median number of GP visits for other illness(es) in the past year was two for cases (interquartile range; IQR 0.5–4) and three for controls (IQR 2–5). This variable was not linear in the logit of case/control status and was therefore collapsed into the binary variable ''child saw a GP for any other illness in the past year'' (75.3% of cases *versus* 91.4% of controls; p=0.001). WIMD quintile was missing for nine participants because their postcodes did not correspond to a WIMD score or they did not provide their home address; this was substituted for the WIMD quintile corresponding to the postcode of their general practice.

Using this procedure, four variables were selected for the final logistic regression model: ''child saw a GP for any other illness in the past year'', home ownership, WIMD quintile, and sex. The model indicated that seeing the GP in the previous year placed children at reduced risk of hospital presentation for pneumonia (adjusted OR 0.28, 95% CI 0.13–0.60; p=0.001). None of the other factors considered were independently associated with this outcome (p>0.05).

Our study is limited by the potential for selection and response bias. Controls were selected for invitation because they had recently consulted a GP for a minor RTI; hence frequent consulters were more likely to be selected than infrequent consulters. However, this control group probably reflects the typical case load of a GP, whereas selecting more infrequent consulters might have resulted in a less representative sample of patients seen by GPs. The low response rate of controls (29.9%) may be a more important limitation. Participants in case–control studies tend to be more health conscious than non-participants [6], thus the carers of controls who took part in the study might be more anxious about their child's health and consult their GP more often. The true association between consulting frequency and hospital presentation for pneumonia or empyema may therefore be weaker than estimated here.

We previously reported that cases consulted a GP significantly more promptly following illness onset (median 2 days; IQR 0–

3 days) compared with controls (median 2 days; IQR 1–5 days) ($p=0.04$) [5], suggesting a more rapid onset of symptoms in children at greater risk of hospital presentation for pneumonia. We now show that the same cases were less likely to have visited a GP for other illnesses in the previous year. The lack of association between these two variables ($p=0.8$) suggests the two findings are unrelated.

We therefore hypothesise that a child presenting to general practice promptly after illness onset, with a history of infrequent consulting, may be at increased risk for pneumonia or empyema. This is consistent with common knowledge regarding any illness that needs prompt and decisive action by the GP. However, our findings cannot inform GP decision making because they may be influenced by response bias. Larger, prospective studies are needed to test our hypothesis.

Joanna C. Crocker*, Colin V.E. Powell#, Kerenza Hood*,¶, Christopher C. Butler* and Meirion R. Evans*

*Institute of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, #Dept of Child Health, Institute of Molecular and Experimental Medicine, School of Medicine, Cardiff University, Cardiff, and ¶South East Wales Trials Unit, School of Medicine, Cardiff University, Cardiff, UK.

Correspondence: J.C. Crocker, Louis Dundas Centre, UCL Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK. E-mail: joanna.crocker@ucl.ac.uk

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REFERENCES

1 Heiskanen-Kosma T, Korppi M, Jokinen C, *et al.* Risk factors for community-acquired pneumonia in children: a population-based case-control study. *Scand J Infect Dis* 1997; 29: 281–285.
2 Teepe J, Grigoryan L, Verheij TJ. Determinants of community-acquired pneumonia in children and young adults in primary care. *Eur Respir J* 2010; 35: 1113–1117.
3 Shah N, Ramankutty V, Premila PG, *et al.* Risk factors for severe pneumonia in children in south Kerala: a hospital-based case–control study. *J Trop Pediatr* 1994; 40: 201–206.
4 Fatmi Z, White F. A comparison of ''cough and cold'' and pneumonia: risk factors for pneumonia in children under 5 years revisited. *Int J Infect Dis* 2002; 6: 294–301.
5 Crocker JC, Powell CV, Evans MR, *et al.* Paediatric pneumonia or empyema and prior antibiotic use in primary care: a case–control study. *J Antimicrob Chemother* 2012; 67: 478–487.
6 Austin H, Hill HA, Flanders WD, *et al.* Limitations in the application of case–control methodology. *Epidemiol Rev* 1994; 16: 65–76.

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Asymmetric dimethylarginine and asthma: results from the Childhood Asthma Prevention Study

To the Editor:

Asymmetric dimethylarginine (ADMA) is a naturally occurring analogue of L-arginine and functions as an endogenous inhibitor of nitric oxide synthase (NOS). ADMA is an established risk factor for cardiovascular disease and contributes to chronic endothelial dysfunction [1]. Recently, it has been proposed that ADMA is also a mediator of allergic airways disease, with animal studies indicating a possible role in the development of airway hyperresponsiveness, lung inflammation and fibrosis. Exogenous administration of ADMA has been shown to augment airway responsiveness to methacholine in murine models of asthma and increased ADMA levels were observed in lung homogenates and sputum specimens from humans with asthma [2]. However, human data on the relationship between ADMA and asthma are limited. Therefore, we examined the relationship between systemic ADMA levels and current asthma in a cohort from the Childhood Asthma Prevention Study (CAPS).

Study subjects included 314 8-year-old children from Sydney, Australia. They were originally enrolled prenatally into a randomised controlled trial of house dust mite avoidance and dietary fatty acid modification implemented from birth to 5 years. All subjects had one or more parents or an older sibling with asthma or wheezing illness. The details of this trial have been published elsewhere [3]. Of the 616 subjects who were enrolled prenatally, 314 had clinical and laboratory