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From the authors:

The authors would like to thank P. Charles for his interest in their recent article [1]. His major point of criticism is that the finding of an association between pre-hospital treatment and outcome may lead to unnecessary antimicrobial usage in the ambulatory setting. P. Charles emphasises the role of host factors on outcome of pneumonia and cites a recent study evaluating community-acquired pneumonia (CAP) treatment failure [2]. Host factors, namely neoplasia and neurological disease, were associated with CAP outcome [2]. However, patients with previous antimicrobial treatment were excluded in the study by GENNE *et al.* [2], thus it is impossible to know the impact of pre-hospital antibiotic therapy on outcome from the study. In our study, a less severe course of pneumococcal disease in patients with prior ambulatory treatment was found [1]. As a randomised trial was not performed, data are clearly observational and open to confounding. Accordingly we did not claim that a causal relationship is proven by these findings. However, we think it worthwhile to discuss these seemingly provocative data as, in the pre-hospital phase of CAP, the duration and impact of treatment delay may be even larger than in the hospital setting, where most guidelines now recommend institution of treatment within 4–8 h after admission or ''as soon as possible'' [3].

Since the mortality of pneumococcal disease has not changed much over the past decades, new options for increasing survival are necessary. Several data, including ours and on the timing of in-hospital treatment [4], suggest a benefit from institution of antimicrobial therapy early in the course of disease. This has to be weighed against the potential of antibiotic misuse as outlined by P. Charles. Obviously more data, especially from randomised trials are needed to draw firm conclusions.

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STATEMENT OF INTEREST

None declared.

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β_2-Adrenoceptor polymorphisms and asthma phenotypes: interactions with passive smoking

To the Editors:

The article of ZHANG *et al.* [1] was of particular interest to us for two reasons. First, this article reported reduced lung function at age 11 yrs in children with arginine 16, compared with those homozygous for glycine 16, among those exposed to tobacco smoke but not in unexposed children. The present authors' report [2] of a similar association of reduced lung function with the presence of the arginine 16 allele was not mentioned in their discussion. Unlike ZHANG *et al.* [1], we also found lung function to be reduced in children with any glutamine 27 alleles. However, in our study of a smaller birth cohort, the association of

TABLE 1 Relation of exhaled nitric oxide (eNO) to β_2-adrenoceptor genotype in a cohort of 10-yr-old children

	Subjects n	eNO ppb	p-value
Arg16Gly			
⩾1 Arg	15	3.99 (3.26–4.90)	0.017
Gly/Gly	21	6.49 (4.70–8.95)	
Glu27Gln			
⩾1 Gln	19	4.21 (3.34–5.30)	0.027
Glu/Glu	17	6.87 (4.82–9.79)	
Haplotype			
⩾1 Arg/⩾1 Gln	19	4.21 (3.34–5.30)	0.027
Gly16Gly/Glu27Glu#	17	6.87 (4.82–9.79)	

Data are presented as geometric mean (95% confidence interval). Arg16Gly: substitution of glycine (Gly) for arginine (Arg) at codon 16; Glu27Gln: substitution of glutamic acid (Glu) for glutamine (Gln) at codon 27. #: linkage disequilibrium occurred since all Glu/Glu genotypes were associated with Gly/Gly.

β_2-adrenoceptor polymorphisms and lung function (maximal expiratory flow at functional residual capacity) was found at 1 month of age, probably before there could be any influence of the post-natal environment. In this small study, no influence of maternal smoking was detected. This association was not found at 10 yrs, but only 26% had a smoking parent. Were any associations between β_2-adrenoceptor polymorphisms and lung function found at birth in the Australian cohort? If not, could population differences or even a more polluted intrauterine environment in the UK cohort explain why this association was only found in later childhood in Australia?

The second point of interest was the unexpected finding of an effect of β_2-adrenoceptor polymorphisms on exhaled nitric oxide in children without smoke exposure. This information was also available from the present authors' study [2], and so we revisited our data, looking specifically at exhaled nitric oxide levels at age 10 yrs and β_2-adrenoceptor genotype. As has been reported before, atopy (any positive skin-prick test result) had a significant effect on exhaled nitric oxide but, surprisingly, β_2-adrenoceptor polymorphisms also showed similar significant effects (table 1). In the general linear model, there was no interaction between genotype and atopy, and no detectable effect of parental smoking. The present results confirm those of ZHANG *et al.* [1], and suggest a sizeable effect since numbers in our study were small. The relevance of this is unclear, but the same occurrence in separate cohorts in different hemispheres suggests that they are real.

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STATEMENT OF INTEREST
None declared.

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From the authors:

As β_2-adrenoceptors (AR) play an important role in the regulation of bronchial smooth muscle tone, finding an association between the functional variation in the β_2-AR gene and lung function would be expected. In the Australian unselected cohort, arginine (Arg) 16 was found to be associated with decreased lung function in children aged 11 yrs who had been exposed to passive smoking [1]. However, in the UK high-risk cohort (at least one atopic parent), no similar association was found for 10-yr-old children [2]. Arg16 was found to be associated with decreased neonatal lung function as measured by maximum flow at functional residual capacity ($V'_{max,FRC}$) in the UK cohort [2]. We also measured $V'_{max,FRC}$ in the Australian population at age 1 month. As we have previously reported [3], $V'_{max,FRC}$ appeared to be lower in individuals homozygous for Arg16, although this difference was not statistically significant. We agree with N.M. Wilson and A. Bush that an, as yet unknown, environmental difference between the Australian and UK cohorts that affects the *in utero* environment may contribute to these inconsistencies.

With regard to the relationship between β_2-AR polymorphisms and exhaled nitric oxide (eNO), we surmised that there were indirect links between β_2-AR and eNO through cytokine regulation or endothelial L-arginine/nitric oxide pathway [1]. Interestingly, in the UK cohort, Arg16 and Glutamine (Gln) 27 were also found to be associated with decreased eNO. This finding in the UK cohort confirms the effects of β_2-AR on eNO in the Australian cohort. More studies need to be conducted in order to elucidate the association between β_2-AR and eNO with respect to pathogenesis of asthma and allergy.

We were interested in the comments of N.M. Wilson and A. Bush as, although there are some differences between the findings of the two birth cohort studies, the similarities are quite striking and strengthen the case that β_2-adrenoceptor polymorphisms play an important role in determining phenotypic features in early life.

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STATEMENT OF INTEREST
None declared.

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