

## EDITORIAL

# Clinical and Experimental Allergy

## Reverse causation and confounding-by-indication: do they or do they not explain the association between childhood antibiotic treatment and subsequent development of respiratory illness?

This article discusses the findings of the paper in this issue by Wickens et al. [2].

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Several studies have investigated the association between antibiotic use during infancy and the subsequent development of respiratory illness. Despite all the efforts investigating this important issue, a firm statement about whether or not there is a causal link between both factors is still lacking. This has much to do with the complex phenomena of 'reverse causation' and 'confounding-by-indication', concepts that will form the basis of this editorial.

For those who are not familiar with these concepts we will give a brief clarification. 'Reverse causation' deals with establishing the causality of an association by assessing the time relation between an exposure and outcome: does the cause (exposure) precede the effect (outcome)? For example, an association between antibiotic intake and respiratory disease may be explained by the fact that the antibiotics were actually prescribed *because of* the respiratory symptoms. This is different from 'confounding-by-indication'. To cause confounding bias, a variable must be a risk factor for a disease among non-exposed persons, must be associated with the exposure of interest in the population from which the cases derive, but must not be an intermediate step in the causal pathway between the exposure and the disease [1]. The implication is that *confounding-by-indication* should refer to those situations in which the indication for treatment acts as a confounder. In those cases, an association between antibiotic intake and respiratory disease may be confounded (explained) by

a third factor that it is *an indication* for antibiotics prescription while at the same time being a risk factor for asthma. Consequently, the validity of epidemiologic research concerning the role of antibiotics intake in relation to the development of respiratory symptoms is affected. 'Confounding-by-indication' in daily epidemiologic practice is sometimes used interchangeably with just 'confounding' or 'reverse causation'.

Because antibiotics are commonly used to treat infections during early childhood, an understanding of the relation between antibiotic use and asthma is critical for health-care professionals and policymakers world-wide. In the present issue of *Clinical and Experimental Allergy*, Wickens et al. [2] report results from a nicely set up birth cohort with impressive response rates at ages 15 months (91%) and 4 years (89%). The authors state that much of the effect of antibiotics on respiratory disease (as found in some previous studies) is due to confounding by chest infections. (Of note, the authors have chosen to use the term 'confounding'.) Does this firm conclusion mean that we have now come at a point in time at which we can stop debating the issue? Is there indeed no true causal effect of childhood antibiotic use and development of asthma and were all previously reported associations due to reverse causation or confounding?

In an attempt to answer this question, we propose to have a look at the current evidence on the topic. Where are we at mid-2008? Positive associations between antibiotic use and childhood respiratory illness have been reported earlier, results mostly coming from retrospective (cross-sectional) studies as reviewed in a recent meta-analysis on antibiotic use in the first year of life by Marra et al. [3]. In many of these retrospective studies the issue of 'reverse causation' remained unresolved: Did antibiotic intake

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actually precede symptoms or were antibiotics prescribed in response to symptoms of wheezy bronchitis? The meta-analysis has reported a two-fold increased risk of childhood asthma following antibiotic use, but only in retrospective studies and not among studies conducted prospectively. Results from retrospective studies could be influenced by recall bias, as individuals with asthma may be more likely to report an exposure to antibiotics in infancy than those without diagnosis of asthma [3]. To make it worse, information regarding potential confounders would also be subject to recall bias. Results from these studies therefore, should always be interpreted with caution.

For this reason, we focus this editorial on four recent *prospective* studies on the topic, including the one published in this issue of *Clinical and Experimental Allergy*, that followed the publication of the meta-analysis and that have indeed addressed the issue of reverse causation.

All four studies found a positive association between antibiotics and respiratory illness in childhood but no indication for reverse causation. Firstly, in 2007 our own group reported in a birth cohort of 2764 infants that after exclusion of infants with wheezy symptoms in the first 6 months of life, antibiotic use in the first half year of life was still associated with an increased risk of recurrent wheeze in the first 2 years [4]. The strength of this study was its prospective nature and reasonable size of the cohort but data was lacking on reasons for antibiotic prescription, infant infections and type of antibiotics taken (broad vs. narrow spectrum). Also in 2007, a longitudinal study was published of a Canadian cohort of 13 980 children using health-care and prescription databases containing data on physician visits, hospitalizations, prescription of drugs, and risk and protective factors for asthma, such as gender, urban or rural location, income, number of siblings, number of health-care visits and maternal history of asthma [5]. The impressive size of the cohort together with the precise recording of disease occurrence, drug description and number of health care visits are important strengths of this study and prevent from recall bias to play a role in the data interpretation. Information on traditional confounders such as pets, parental smoking or smoking during pregnancy, diet and others are, however, generally missing in this kind of databases. The study investigated the association between antibiotic prescription in the first year of life and asthma at age 7. In a model that took into account reverse causation by excluding from the analyses children who had received asthma diagnoses during the first year of life ( $n = 864$ ), asthma was significantly more likely to develop in children receiving antibiotics in a dose-dependent manner [5]. Very recently in April 2008, a Swedish group published the results of a study into neonatal antibiotic treatment and early wheezing at 12 months of age [6]. The antibiotic treatment in these infants was started immediately after arriving to the neonatal ward after transfer

from the delivery room or maternity ward on the first day (in some occasions first days) of life (personal communication with author). The researchers found a positive association between neonatal antibiotic treatment and early wheezing at age 12 months.

Undoubtedly, the antibiotics in this study had been prescribed before the first symptoms of wheeze would develop. However, this study did not report data on type of antibiotics taken (narrow vs. broad spectrum) and reasons for admission to the neonatal ward, so that confounding-by-indication related to reasons for admission cannot be ruled out. Finally, Wickens and colleagues in this issue of *Clinical and Experimental Allergy*, report an association between antibiotics in early infancy (first 3 month of life) and asthma symptoms in the first 15 months of life [2] allowing a small overlap between exposure and outcome occurring in the first 3 months of life only. This illustrates that also in this study reversal causation had been taken into account. However, this association disappeared after controlling for number of chest infections and even more after additional adjustment for traditional confounders for asthma such as gender, ethnicity, a family history, parity and ear infection.

Apparently recent good quality designed prospective studies showed that the positive association for antibiotic treatment and respiratory illness still exists after making sure that the antibiotic exposure would precede the outcomes of interest measured. In other words, the association was not explained by reverse causation.

This brings us to the second concept that was mentioned earlier, that of confounding-by-indication. In early childhood asthma-like symptoms are not as yet clearly distinctive from respiratory infections and transient symptoms of wheezy bronchitis. Owing to a difficult differential diagnosis in general practice between bacterial and viral infections, antibiotics in infancy are often prescribed for viral infections [7]. Respiratory Syncytial Virus (RSV) and rhinovirus (RV) infections are strongly associated with infant wheeze in the first year of life [8], and antibiotic use may simply be a marker for viral infections. If the association between early antibiotic use and subsequent development of asthma in childhood is true, the association should be present in children without any respiratory tract indications.

Several studies have attempted to address this issue. In the study of our group, all analyses were adjusted for fever episodes in the first half year of life, which was the same time interval as antibiotic use was measured (as a marker for infections) [4]. This did not change the results (the association between antibiotics and early wheeze remained). We do realize, however, that preferably we would want more precise measurements of infection episodes. The study of Kozyskyj et al. [5], however, was able to show that asthma at age 7 year was almost twice as likely in children receiving one or more antibiotic prescriptions

for *non-respiratory* tract infections in comparison with children who had not received antibiotics. However, further analyses showed that no association with antibiotic use was present in children living in urban settings and that an association with antibiotic use was only present for rural children. Even if Alm et al. in their study showed no evidence for reverse causation to explain their positive association between antibiotic use and wheeze at age 1, the issue of confounding-by-indication remains unresolved from these data. There may be a possibility that the reasons for the antibiotic use were related to risk factors for wheeze [6]. The results from Wickens et al. in this issue show that in their study associations between antibiotic use and asthma in the first 15 months of age were explained by chest infections since birth. We agree with the authors that much of the effect of antibiotics on respiratory disease was due to confounding by chest infections. (Although we would have chosen to refer to this as confounding-by-indication.)

Taken together, the data presented in the peer reviewed literature as per mid-2008 show that it is increasingly unlikely that antibiotic use in childhood increases the risk of asthma later in life via a true causal relationship. Because wheeze and asthmatic symptoms in early childhood are difficult to distinguish from respiratory tract infection, confounding-by-indication is a very plausible explanation for the reported associations.

But how do we move forward from here? For future research in this field, we would recommend to focus more intensively on hypothesis-driven research instead of association-finding research. An often stated hypothesis for the association between antibiotics and asthma is the 'microflora hypothesis': perturbations in the gastrointestinal microflora due to antibiotic use in 'industrialized' countries may disrupt the normal microbiota-mediated

mechanisms of immunological tolerance in the mucosa [9]. Therefore, investigating how exactly antibiotics may modify the gut microbiota and influence respiratory illness may be an interesting field of research. Also, which underlying symptoms (e.g., symptoms from rhinovirus and respiratory syncytial virus [RSV] infections) are causally linked to the development of asthma, and why, are imperative questions to be answered in the near future.

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