

# Antibiotic exposure in early life and development of childhood asthma

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## Abstract

**Question** I understand that antibiotic use in children younger than 2 years of age has been associated with the development of asthma. With so many children in early life suffering from middle ear and throat infections, are those children who are treated with antibiotics at higher risk of developing asthma or exacerbating their asthma? Is there a relationship between number of antibiotic courses and risk of asthma?

**Answer** Administration of antibiotics in the first 2 years of life has been shown to be associated with asthma later in life in retrospective and prospective studies. However, study limitations such as protopathic bias, poor data collection methods, and small cohort size prevent clear determination of causality between antibiotics and asthma. The use of antibiotics in young children warrants careful consideration due to antibiotic resistance, adverse effects, and potential association with asthma.

## Exposition aux antibiotiques tôt dans la vie et développement de l'asthme infantile

### Résumé

**Question** Je sais que l'utilisation d'antibiotiques chez les enfants de moins de 2 ans a été associée au développement de l'asthme. Étant donné le grand nombre d'enfants qui souffrent tôt dans leur vie d'infections de l'oreille moyenne et de la gorge, ces enfants traités aux antibiotiques courent-ils un risque plus élevé de développer de l'asthme ou d'exacerber un problème existant? Y a-t-il des liens entre le nombre de séries d'antibiotiques et le risque d'asthme?

**Réponse** Il a été démontré dans des études rétrospectives et prospectives que l'administration d'antibiotiques durant les 2 premières années de vie était associée à l'asthme plus tard dans la vie. Par ailleurs, des limites dans les études, comme un biais protopathique, des méthodes médiocres de collecte de données et la petite taille des cohortes, empêchent de déterminer clairement la causalité entre les antibiotiques et l'asthme. L'utilisation des antibiotiques chez les jeunes enfants mérite d'être envisagée avec précaution en raison de la résistance aux antibiotiques, des effets indésirables et d'une association potentielle avec l'asthme.

**A**sthma is one of the most prevalent chronic conditions worldwide, affecting around 10% of children in developed nations.<sup>1</sup> Rates of asthma in children have been on the rise since 1980 along with an increase in the use of antibiotics in children with confirmed or suspected bacterial infections.<sup>2</sup>

Asthma is a multifactorial condition associated with allergy, environmental exposure, and genetic predisposition.<sup>3-5</sup> Recent studies have suggested that asthma in children is linked to increased exposure to antibiotics during the first 2 years of life.<sup>3,6-8</sup> Early exposure to antibiotics might alter intestinal microbiota and cause a microbial imbalance.<sup>9,10</sup> Furthermore, early-life exposure to antibiotics has been reported to disrupt immune system development.<sup>11</sup> The microbiota of the gut play a crucial role in the development of CD4<sup>+</sup> T cells, which differentiate into the helper T cells T<sub>H</sub>1 and T<sub>H</sub>2.<sup>12</sup> Exposure to antimicrobial medication delays postnatal

T<sub>H</sub>1 maturation, which reduces the T<sub>H</sub>2 response that is characteristic of allergy.<sup>1,4,13</sup> Therefore, the administration of antibiotics is hypothesized to disrupt immune function and increase the risk of atopy later in life by inappropriately producing immune factors.<sup>11</sup>

### Notable biases

For decades, the scientific community has explored the relationship between antibiotic exposure and asthma development through parental questionnaires and epidemiologic databases.<sup>1,3,5,8</sup> Important limitations include use of small cohorts,<sup>14</sup> incomplete data,<sup>4</sup> sampling biases in questionnaires and data records,<sup>2,5</sup> protopathic bias (exposure to antibiotics in response to asthma symptoms),<sup>1</sup> difficulty differentiating the effect of antibiotics from the effect of infection itself on exacerbation of asthma,<sup>3</sup> and inherent increased risk of atopic asthma.<sup>10</sup>

## Evidence for association

A prospective, longitudinal cohort study of 4777 Swedish children asked parents to complete questionnaires when their child was 6 months and 1, 4, 8, and 12 years of age.<sup>5</sup> On the questionnaire, asthma was defined as those conditions, treatments, and symptoms as diagnosed by a doctor. Cumulative prevalence of asthma was 14% (397 of 2913) for those receiving antibiotics in the first week of life.<sup>5</sup> Similarly, among 1401 children in 56 private and 15 public clinics in New England, dose-related correlation between 1 course of antibiotics before 6 months of age and asthma was seen, with an odds ratio (OR) of 1.40 (95% CI 0.90 to 2.15) and an OR of 1.72 (95% CI 1.11 to 2.65) for 2 or more courses.<sup>1</sup> Both studies linked asthma to antibiotic use in the first 6 months of life, but did not adjust for meaningful cofactors that might have led to the development of asthma.

Three large administrative data sets (using International Classification of Diseases, Ninth Revision codes) provided further evaluation of antibiotic use and asthma in childhood. In British Columbia between 1997 and 2003, 43% of 250 000 newborns were prescribed at least 1 antibiotic course during their first year of life; asthma was associated with antibiotic use, with a positive adjusted hazard ratio (HR) of 1.12 (95% CI 1.08 to 1.16).<sup>2</sup> Rates increased with more than 4 courses (adjusted HR of 1.30; 95% CI 1.20 to 1.41).<sup>2</sup> Furthermore, oral antibiotic use in the first year of life in 13 116 children from Manitoba was associated with asthma at age 7 in both urban and rural settings ( $P=.04$ ).<sup>7</sup> Findings also suggested that broad-spectrum antibiotics were more likely to be associated with asthma (OR=1.50; 95% CI 1.16 to 1.93) compared with narrow-spectrum antibiotics (OR=1.35; 95% CI 0.29 to 6.23).<sup>7</sup> In almost 35 000 Italian children with asthma, having 1 or more courses of antibiotics during the first 12 months of life was associated with a positive incidence rate ratio of 1.51 for asthma at 13 to 35 months (95% CI 1.48 to 1.54).<sup>8</sup> The asthma rate for those 6 years of age and older was 35% higher among children who were exposed to antibiotics in the first year of life.<sup>8</sup>

In the United Kingdom, almost 5000 children who were given antibiotics before 24 months of age were more likely to have asthma by 91 months (treated from 0 to 6 months, OR=1.12, 95% CI 0.72 to 1.74; 6 to 15 months, OR=1.13, 95% CI 0.81 to 1.56; 15 to 24 months, OR=1.50, 95% CI 1.08 to 2.07).<sup>4</sup> Similarly, in almost 80 000 American children aged 2 years and younger across 13 states, 1 to 2 courses of antibiotics were associated with an increased risk of asthma (HR=1.34; 95% CI 1.21 to 1.49), and 3 or more courses posed an even greater risk (HR=1.71; 95% CI 1.54 to 1.90).<sup>3</sup> As shown by these 2 studies, both the time of antibiotic administration and the number of courses might play a role in the development of asthma.

In contrast, findings from approximately 4500 children across 14 health centres who were followed from birth to 5 years of age in Arizona revealed a negative correlation

between antibiotics and asthma.<sup>15</sup> Antibiotics were prescribed more to children with asthma at 2 years of age than to those without asthma at 2 years of age; this could be owing to cases of lower respiratory tract illnesses (LRIs) and upper respiratory tract illnesses (URIs) found in children who had asthma at age 2 years.<sup>15</sup> An OR of 1.1 (95% CI 0.8 to 1.4) between those children who received 1 to 2 courses of antibiotics and those who did not indicated no significant association between antibiotics and asthma.<sup>15</sup> In Western Australia, almost 200 children with genetic atopic risk (having at least 1 parent with a diagnosis of asthma) were prospectively followed for 5 years using parental daily diaries.<sup>16</sup> Among this cohort, children presenting with a wheezing LRI in the first 7 to 12 months of age were more likely to be prescribed antibiotics than children presenting with a nonwheezing LRI or URI were (OR=2.3; 95% CI 1.3 to 3.8).<sup>16</sup> Both studies highlight the importance of differentiating asthma from LRIs or URIs, given the increase in asthma worldwide.<sup>1</sup>


## Exacerbation of asthma

Differentiating between development of asthma and exacerbation of existing asthma has been challenging in research. Data from 4 other large cohorts of children who were prescribed antibiotics in the first 3 years of life revealed more of a risk of asthma with early-life antibiotic use (OR=2.18; 95% CI 1.04 to 4.60), but found no association between antibiotics and risk of asthma exacerbations (OR=0.93; 95% CI 0.65 to 1.32).<sup>6</sup> Furthermore, a meta-analysis of observational pediatric studies found 4 prospective and 4 retrospective studies comparing at least 1 antibiotic course to none in more than 12 000 children (1817 with asthma); data from more than 27 000 children (3392 with asthma) were included for a dose-response analysis.<sup>17</sup> The pooled OR was 2.05 (95% CI 1.41 to 2.99), with a significantly stronger association in the retrospective studies (OR=2.82; 95% CI 2.07 to 3.85) than the prospective studies (OR=1.12; 95% CI 0.88 to 1.42).<sup>17</sup> The overall OR for dose-response analysis was 1.16 (95% CI 1.05 to 1.28) for each additional course of antibiotics.<sup>17</sup>

Even while addressing confounding by indication, smoking during pregnancy, first-degree relatives with asthma, antibiotic use while pregnant, and race, a study of 300 mothers in urban Chicago, Ill, still showed a significant OR between antibiotics and both asthma (OR=1.58; 95% CI 1.27 to 1.96) and wheezing (OR=1.29; 95% CI 1.07 to 1.55).<sup>18</sup> After adjusting for reverse causation, the study showed that there was an association between asthma with wheezing and antibiotic use for respiratory reasons, but it was not significant ( $P=.08$ ).<sup>18</sup>

## Conclusion

Extensive longitudinal studies associate the exposure to antibiotics with development of asthma in young children. However, these investigations are limited to cohort studies and there is some variation in outcomes. Traditional

reasons for antibiotic supervision, such as avoiding antibiotic resistance and health care expense, remain paramount; therefore, further caution and prescribing only for those in need is critical to avoid the potential increased risk of asthma. 

#### Competing interests

None declared

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#### References

- Risnes KR, Belanger K, Murk W, Bracken MB. Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children. *Am J Epidemiol* 2011;173(3):310-8. Epub 2010 Dec 29. Errata in: *Am J Epidemiol* 2011;173(7):846, *Am J Epidemiol* 2011;173(12):1475.
- Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskij A, Patrick DM, et al. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* 2009;123(3):1003-10.
- Fishman E, Crawford G, DeVries A, Hackell J, Haynes K, Helm M, et al. Association between early-childhood antibiotic exposure and subsequent asthma in the US Medicaid population. *Ann Allergy Asthma Immunol* 2019;123(2):186-92.e9. Epub 2019 May 31.
- Hoskin-Parr L, Teyhan A, Blocker A, Henderson AJW. Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: a dose-dependent relationship. *Pediatr Allergy Immunol* 2013;24(8):762-71. Epub 2013 Dec 2.
- Strömberg Celind F, Wennergren G, Vasileiadou S, Alm B, Goksör E. Antibiotics in the first week of life were associated with atopic asthma at 12 years of age. *Acta Paediatr* 2018;107(10):1798-804. Epub 2018 Apr 16.
- Ahmadizar F, Vijverberg SJH, Arets HGM, de Boer A, Turner S, Devereux G, et al. Early life antibiotic use and the risk of asthma and asthma exacerbations in children. *Pediatr Allergy Immunol* 2017;28(5):430-7. Epub 2017 Jun 8.
- Kozyrskij AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest* 2007;131(6):1753-9. Epub 2007 Apr 5.
- Pitter G, Ludvigsson JF, Romor P, Zanier L, Zanotti R, Simonato L, et al. Antibiotic exposure in the first year of life and later treated asthma, a population based birth cohort study of 143,000 children. *Eur J Epidemiol* 2016;31(1):85-94. Epub 2015 May 9.
- Ni J, Friedman H, Boyd BC, McGurn A, Babinski P, Markossian T, et al. Early antibiotic exposure and development of asthma and allergic rhinitis in childhood. *BMC Pediatr* 2019;19(1):225.
- Fujimura KE, Lynch SV. Microbiota in allergy and asthma and the emerging relationship with the gut microbiome. *Cell Host Microbe* 2015;17(5):592-602.
- Di Cicco M, Pistello M, Jacinto T, Ragazzo V, Piras M, Freer G, et al. Does lung microbiome play a causal or casual role in asthma? *Pediatr Pulmonol* 2018;53(10):1340-5. Epub 2018 Jun 26.
- Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012;3(1):4-14. Epub 2012 Jan 1.
- Yamamoto-Hanada K, Yang L, Narita M, Saito H, Ohya Y. Influence of antibiotic use in early childhood on asthma and allergic diseases at age 5. *Ann Allergy Asthma Immunol* 2017;119(1):54-8.
- Su Y, Rothers J, Stern DA, Halonen M, Wright AL. Relation of early antibiotic use to childhood asthma: confounding by indication? *Clin Exp Allergy* 2010;40(8):1222-9. Epub 2010 Jun 7.
- Celedón JC, Fuhlbrigge A, Rifas-Shiman S, Weiss ST, Finkelstein JA. Antibiotic use in the first year of life and asthma in early childhood. *Clin Exp Allergy* 2004;34(7):1011-6.
- Kusel MM, de Klerk N, Holt PG, Sly PD. Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy* 2008;38(12):1921-8.
- Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. *Chest* 2006;129(3):610-8.
- Lapin B, Piorkowski J, Ownby D, Wagner-Cassanova C, Freels S, Chavez N, et al. The relationship of early-life antibiotic use with asthma in at-risk children. *J Allergy Clin Immunol* 2014;134(3):728-9. Epub 2014 Jun 19.



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