

Higher risk of allergies at 4-6 years of age after systemic antibiotics in the first week of life

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To the editor,

In humans, the first 100 days appear to be a "critical window" of colonization during which microbial communities shape immune maturation.^{1,2} The use of antibiotics early in life may disrupt the normal maturation process leading to adverse health outcomes such as atopic disorders^{1,3-5}. The effects of antibiotic exposure immediately in the first week of life have rarely been investigated, nor the differences between treatment of 2-3 days and a prolonged treatment of 5-7 days. In the INCA study, a prospective birth cohort study of 151 infants receiving broad-spectrum antibiotics in their first week of life (AB+), and 285 healthy controls (AB-), we previously showed that antibiotic treatment in the first week of life was associated with an increased risk of wheezing, infantile colic and a trend towards more allergic sensitization in the first year of life⁶. The aim of this follow-up study in 418 eligible children was to determine if antibiotic treatment in the first week of life in term-born children was associated with an increase in atopic disorders at 4-6 years of age, using ISAAC questionnaires filled out by parents, ICDPC codes derived from general physicians, and pharmaceutical records from local pharmacies. Detailed information regarding the subjects and methods is described in the online Appendix.

In total, 341 of 418 (82%) questionnaires were filled out (114 AB+ and 227 AB-), Parental reported allergy was significantly higher in AB+ vs AB- children (23% vs 11% respectively, $p=0.003$) as was doctor-diagnosed allergy (12% vs 4% respectively, $p=0.008$). Confirmed food allergies were more common in AB+ children compared with AB- children (10 vs. 4% respectively, $p=0.03$). After correcting for sex, age, daycare attendance, family atopy, and parental level of education, parental-reported allergy was clearly associated with antibiotics use in the first week of life (aOR 2.40 [95%CI 1.22-4.72, $p=0.01$]). Additional adjustment for treatment duration showed that only 5-7 and not 2-3 days AB treatment was associated with a higher risk of parental reported allergy (aOR 2.85 [95%CI 1.37-5.91, $p=0.005$]). More importantly, this effect was independent of exposure to acid-suppressive drugs or additional antibiotics in the first two years of life (36% and 35% in AB- and AB+ group, respectively). The prevalence of eczema, wheezing/asthma, or allergic rhinitis was not different between AB+ and AB- children (Table 2).

These results suggest that very early exposure to AB in the first week of life has a higher impact on microbiota and immune development than when administered later in childhood. It also emphasizes the need for judicious use of AB in neonates, especially prolonged treatment of 5-7 days. Moreover, our findings accentuate the need for finding strategies to modify microbiome development after AB exposure to minimize

aberrant immune development.

Strengths of this study are the prospective design, the high response rate (82%), and the combined information collected from doctors and pharmacists, contributing to the reliability of the reported results, which allowed us to distinguish between the effect of antibiotics within and after the first week of life. A limitation of the study is the 4-6-year follow-up, which may have been too short for diagnosing asthma and allergic rhinitis.

In conclusion, the risk of having an allergy at 4-6 years of age increased nearly 3-fold in children after antibiotic treatment for 5-7 days in their first week of life, independent of later AB treatment. These long-term adverse health effects of neonatal antibiotic use emphasize the need to implement AB stewardship programs to avoid AB overuse and reduce the duration of AB treatment where possible in the first week of life.

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Conflict of interest

The authors declare no conflict of interest in relation to this work.

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Authorship

Kim Kamphorst: conception and design, acquisition of data, analysis and interpretation of data; drafting the manuscript, approval of final version of the manuscript

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Ruurd M. van Elburg: conception and design, analysis and interpretation of data; drafting the manuscript, approval of final version of the manuscript

Table 1: baseline characteristics

	AB- N=227	A
Age median (IQR)*	5 (4.6-5.9)	4
Sex (male n,%)	122 (54)	6
BMI mean (SD)	15.6 (1.5)	1
Delivery mode* n (%) Vaginal C-Section	146 (64) 81 (36)	8
Breastfeeding Median duration (IQR) Median duration exclusive (IQR)	4 (1-8) 2 (0-5)	2
Pets n (%) No Cat Dog Cat + dog Other	84 (37) 59 (26) 37 (16) 23 (10) 24 (11)	4
Daycare attendance n (%) No <3 months 3-6 months >6 months	73 (32) 25 (11) 99 (44) 30 (13)	3
Siblings n (%) Yes No Missing	120 (53) 100 (44) 7 (3)	6
Parental atopic disease n (%) Yes No Missing	141 (62) 79 (35) 7 (3)	6
Highest level of education n (%) Low/middle High Unknown	44 (19) 174 (77) 9 (4)	2
Number of courses in the first year of life (first week excluded) median (IQR) ¹	0 (0-1)	0
AB free months in the first year of life* ¹ (first week excluded) median (IQR)	9 (7-11)	7
Number of courses after first week in the first 2 years ² median (IQR)	1 (1-2)	1
Eczema first year of life n (%) Yes No	79 (35) 148 (65)	4

AB-: no antibiotics in the first week of life; AB+: antibiotics in the first week of life, for 2-3 days (AB2) or 5-7 days (AB7). *Significant difference between AB+ and AB- by independent t-test and non-parametric test as appropriate ¹ Parental reporting, collected prospectively every month during the first year of life.² Parental reporting, collected retrospectively during the follow-up.

Table 2: incidence of atopic disorders

	AB- N = 227 N, %	AB+ N = 114 N, %	Significance
Parental reported allergy	24 (11)	26 (23)	P=0.003
Wheezing/ Asthma	51 (22)	33 (29)	P=0.206
Eczema	66 (29)	33 (29)	P=0.94
Allergic rhinitis	48 (21)	25 (22)	P=0.90

	AB- N = 227 N, %	AB+ N = 114 N, %	Significance
Doctor diagnosed allergy*	10 (4)**	14 (12)**	P=0.008
Inhalation allergy	4 (2)	6 (5)	P=0.10
Drug allergy	0 (0)	1 (1)	P=0.35
Food allergy	8 (4)	11 (10)	P=0.03
Hazelnut	1 (0.5)	5 (4)	P=0.02
Walnut	1 (0.5)	5 (4)	P=0.02

AB-: no antibiotics in the first week of life; AB+: antibiotics in the first week of life. Significance determined by independent t-test. *Confirmed through skin prick test, blood test and/or provocation test; **6 children have multiple allergies (4 in AB+ and 2 in AB-)