

# Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: The International Study of Asthma and Allergies in Childhood (ISAAC)

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**Background** It has been hypothesized that antibiotic use early in life may increase the subsequent risk of asthma. We have conducted an ecologic analysis of the relationship between antibiotics sales and the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in 99 centres from 28 countries.

**Methods** Data for antibiotics sales for 28 countries were obtained from the Institute for Medical Statistics (IMS), Health Global Services, UK and converted to defined daily doses (DDD). Data on the prevalence of symptoms of asthma, rhinitis, and eczema in 13–14 year olds were based on the responses to the written and video questionnaires from the International Study of Asthma and Allergies in Childhood (ISAAC). The analysis was adjusted for gross national product (GNP) as an estimate of the level of affluence.

**Results** In general, there was a positive association between per capita antibiotics sales and the prevalence of symptoms for asthma, rhinitis, and eczema, but the associations generally became negative once the analyses had been adjusted for GNP. In particular, there were non-significant negative associations between total antibiotics sales and the prevalence of wheeze ever, wheeze in the last 12 months, nose problems with itchy-watery eyes, itchy rash in the last 12 months, and eczema ever. On the other hand there were weak non-significant positive associations for asthma ever, nose problems ever, nose problems in the last 12 months, and itchy rash ever. There was a statistically significant positive association with wheeze at rest as measured by the asthma video questionnaire; however, even this association was weak and would not account for more than a 1% difference in asthma prevalence between countries.

**Conclusions** These findings are generally not consistent with the hypothesis that antibiotic use increases the risk of asthma, rhinitis, or eczema. If there is a causal association of antibiotic use with asthma risk, it does not appear to explain the international differences in asthma prevalence.

**Keywords** Allergies, asthma, children, ecological, eczema, rhinitis, wheeze, antibiotics, ISAAC

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It is well established that asthma prevalence is increasing, and it is a major research priority to ascertain the causes of these striking increases.<sup>1,2</sup> Recent research has shifted attention from allergens that may cause sensitization and/or provoke asthma attacks to factors that may 'programme' the initial susceptibility to atopy and/or asthma.<sup>3</sup> In particular, the 'hygiene hypothesis' postulates that growing up in a more hygienic environment

with less microbial exposure may enhance atopic (TH<sub>2</sub>) immune responses, whereas microbial pressure would drive the response of the immune system—which is known to be skewed in an atopic TH<sub>2</sub> direction during fetal and perinatal life—into a TH<sub>1</sub> direction and away from its tendency to develop atopic immune responses.<sup>4,5</sup> This would protect against atopy and allergic (but not non-allergic) asthma. Several studies have shown a direct association between infections (e.g. hepatitis A, measles) or vaccination with BCG and a lower prevalence of atopy and allergies.<sup>6–9</sup> However, the results for airborne viruses (measles, mumps, rubella, and chickenpox) and BCG vaccination were inconsistent.<sup>10–13</sup> The role of respiratory viral infections is also not very clear; respiratory tract infections are known to exacerbate pre-existing asthma and may also be a risk factor for developing asthma.<sup>14–17</sup>

A corollary of the hygiene hypothesis is that antibiotic use may increase the risk of asthma by reducing the protective effect of bacterial infections and/or disruption of the normal gut bacterial flora.<sup>18,19</sup> However, the epidemiological evidence of an association between exposure to antibiotics (as well as infection) and the development of asthma has been conflicting.<sup>20–28</sup> Several, but not all, studies indicate an association of antibiotic use early in life with the subsequent development of asthma, hay fever, and eczema. The key issue is whether these observed associations are causal, or whether they are due to reverse causation in that the use of antibiotics may be the consequence of an increased occurrence of respiratory infections in children having an asthmatic or allergic predisposition. In this regard, despite the well-known limitations of ecologic studies,<sup>29</sup> there are some potential benefits of such studies since there is perhaps less concern about the possibility of reverse causation, although there will be the usual concerns about other biases associated with ecologic studies.<sup>29</sup> If two populations have the same infection rates and the same rates of antibiotic usage, then a spurious association between antibiotic use and asthma occurrence may occur in studies of individuals within those populations (because of the problem of reverse causation) but this will not produce a bias in comparisons between populations. We have therefore conducted an ecologic analysis of the relationship between antibiotics sales and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema based on the responses to the written and video questionnaires from the International Study of Asthma and Allergies in Childhood (ISAAC).<sup>30–34</sup>

## Methods

The analysis was based on the data for 13–14 year olds from ISAAC.<sup>30–34</sup> The study involved 463 801 children in this age group in 155 collaborating centres in 56 countries (of these, 304 796 were in the 99 centres in 42 countries which used the optional asthma video questionnaire). However, the analyses were confined to those countries in which antibiotic sales data were available. These comprised 99 centres in 28 countries. The first centre survey took place in 1991 but most of the data were collected during the period 1994–1995.<sup>32</sup>

Data for national sales of antibiotics from 28 countries worldwide for 1995 were obtained from the Institute for Medical Statistics (IMS Health, IMS MIDAS (1995); copyright 2002 IMS Health or its affiliates; all rights reserved). IMS data are collected from a number of sources but almost all estimates

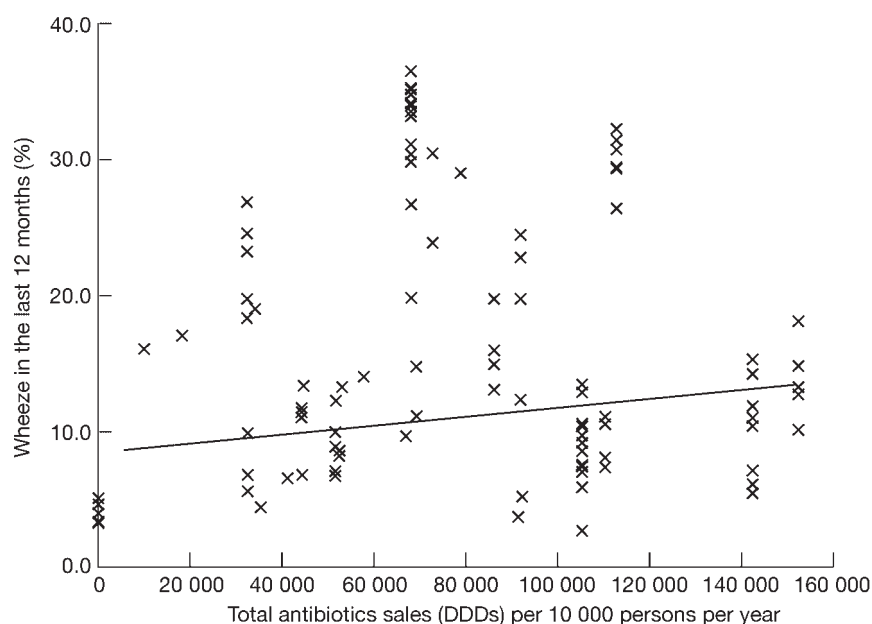
for sales are based on monthly audits collected at the manufacturing or trade level by collecting information from wholesalers and pharmacies. Countries included were from Western Europe (8), Northern and Eastern Europe (4), Eastern Mediterranean (2), Latin America (4), Africa (1), Asia-Pacific (6), Oceania (1), and North America (2). Data were available on total antibiotic sales, as well as data for broad spectrum, narrow spectrum, and ‘other’ antibiotics. For ease of comparison the amount of antibiotics was converted to defined daily doses (DDD). The DDD is a unit based on the average daily dose used for the main indication of the drug.<sup>35</sup> Overall, 76% of all antibiotic sales were for broad spectrum antibiotics, 23% were for narrow spectrum antibiotics, and less than 1% were for ‘other’ antibiotics. We therefore conducted separate analyses for broad spectrum, narrow spectrum, and total antibiotic sales. The average number of DDD of antibiotics sold was 3.3 per person per year, with the highest rate in France (14.8 per year) and the lowest in China (0.07 per year).

The analyses involved the key questions on the prevalence of symptoms of asthma, rhinitis, and eczema from the ISAAC questionnaires.<sup>30</sup> The key asthma questions used were those on ‘wheeze ever’, ‘wheeze in the last 12 months’, and ‘asthma ever’, and the key video asthma question used was the sequence on ‘wheeze at rest in the last 12 months’ from the ISAAC video questionnaire. The key rhinitis questions used were those on ‘nose problems ever (sneezing or runny or blocked nose)’, ‘nose problems in the last 12 months’, and ‘nose problems with itchy-watery eyes in the last 12 months’.<sup>33</sup> The key eczema questions used were those on ‘eczema ever’, ‘itchy rash ever’ (coming and going for ≥6 months), and ‘rash in the last 12 months’.<sup>34</sup>

For each of these questions, the data were analysed by linear regression with one data point for each centre, weighted by the inverse variance of the prevalence estimate for the centre, and adjusted for the gross national product (GNP) of the country in which the centre was based. The level of ‘Westernization’ or ‘affluence’ of a country was considered to be a potential confounder, since this was found to be associated with asthma prevalence in the ISAAC study, and because Westernization involves changes in lifestyle and environmental exposures that could be related to asthma risk. The analyses were therefore adjusted for GNP because this is a readily available marker for the level of affluence and ‘Westernization’ of a country.

## Results

In the unadjusted analyses, there was a positive correlation between per capita antibiotics sales and the prevalence of symptoms for asthma, rhinitis, and eczema. For example, Figure 1 shows the pattern for total antibiotic sales and the prevalence of wheeze in the last 12 months. However, the associations were generally negative once the analyses had been adjusted for GNP (Table 1). For example, Table 1 shows that there was actually a non-significant negative association of total antibiotic sales and the prevalence of wheeze in the last 12 months (‘current wheezing’) once the analyses were adjusted for GNP. For example, the coefficient for total antibiotic sales and current wheezing was 0.42 in the crude analysis ( $P = 0.08$ ) and  $-0.29$  ( $P = 0.21$ ) in the adjusted analyses (Table 1). The adjusted estimate indicates that a one-unit increase in per capita sales of total antibiotics was associated with a decrease of 0.29% in the



**Figure 1** Total antibiotics sales in defined daily doses (DDD) per 10 000 population per year and (unadjusted) prevalence of wheeze in the last 12 months

**Table 1** Regression analysis of the prevalence of symptoms of asthma, rhinitis, and eczema (by centre) against per capita antibiotic sales, adjusted for gross national product (GNP), and weighted by the inverse variance of the prevalence in each centre (n = 99 for all analyses except n = 97 for the eczema questions and n = 61 for the video asthma questionnaire)

Symptom	Total antibiotics			Broad spectrum			Narrow spectrum		
	Coefficient	SE	P-value	Coefficient	SE	P-value	Coefficient	SE	P-value
<b>Written asthma questionnaire</b>									
Wheeze ever	-0.40	0.36	0.28	-0.37	0.46	0.43	-2.25	1.46	0.13
Wheeze in last 12 months	-0.29	0.23	0.21	-0.29	0.29	0.32	-1.66	0.92	0.08
Asthma ever	0.11	0.17	0.50	0.21	0.21	0.32	-0.26	0.68	0.71
<b>Video asthma questionnaire</b>									
Wheeze at rest in last 12 months	0.35	0.13	0.01	0.48	0.16	<0.01	0.67	0.58	0.25
<b>Rhinitis questionnaire</b>									
Nose problems ever <sup>a</sup>	0.31	0.32	0.34	0.37	0.41	0.36	0.75	1.31	0.57
- in last 12 months	0.13	0.28	0.63	0.20	0.35	0.57	-0.40	1.13	0.73
- with itchy-watery eyes in last 12 months	-0.05	0.15	0.76	-0.04	0.19	0.85	-0.34	0.64	0.59
<b>Eczema questionnaire</b>									
Itchy rash ever	0.38	0.22	0.86	0.004	0.27	0.99	0.39	0.90	0.66
Itchy rash in last 12 months	-0.13	0.17	0.46	-0.16	0.21	0.44	-0.45	0.70	0.52
Eczema ever	-0.16	0.25	0.52	-0.33	0.31	0.30	0.38	0.93	0.68

<sup>a</sup> Sneezing or runny or blocked nose.

prevalence of wheeze in the last 12 months (coefficient = -0.29, SE = 0.23,  $P = 0.21$ ). Therefore a country with no antibiotic use would have a decreased asthma prevalence of about 1% (3.3 times 0.29%) compared with a country with the mean usage of 3.3 daily doses per capita.

There were non-significant negative associations between total antibiotics sales and the prevalence of wheeze ever, wheeze in the last 12 months, nose problems with itchy-watery

eyes, itchy rash in the last 12 months, and eczema ever. On the other hand there were non-significant positive associations for asthma ever, nose problems ever, nose problems in the last 12 months, and itchy rash ever. The one significant positive association was for wheeze at rest in the last 12 months as measured by the ISAAC video questionnaire, although this analysis was based on a smaller number of centres (61) than for the written questionnaire analyses (99 centres).

We also conducted several sub-analyses in order to investigate possible sources of bias. The asthma prevalence data were available for each centre, but the antibiotics sales data were only available for each country. We therefore conducted an analysis in which the 99 centres were grouped into the 28 countries. This made little difference to the findings; for example, the adjusted coefficient for total antibiotics for current wheezing was  $-0.29$  in the overall analyses based on the 99 centres (Table 1) and  $-0.23$  in the analyses based on the 28 countries. We also conducted separate analyses for antibiotic suspensions since these may be used more commonly in children. We acknowledge, however, that antibiotics suspensions are equally dispensed to elderly people and patients with difficulty taking capsules or tablets orally and therefore may not be the ideal proxy measure for early childhood use of antibiotics. This made little difference to the findings for asthma, although the adjusted findings for eczema became positive (and statistically significant). Finally, we conducted an analysis confined to the 61 centres that included the video in order to investigate the reasons for the differences between the findings for the written and video questionnaires (Table 1). In this analysis, all of the adjusted coefficients were positive (as for the video questionnaire as shown in Table 1) but only the findings for 'asthma ever' and 'nose problems ever' were statistically significant. These findings indicate that the findings are consistent between the written and video questionnaires, and that the apparent differences in Table 1 are due to the smaller number of centres involved in the video questionnaire analyses. These are particularly affected by the UK centres which did not use the video questionnaire and which had the highest asthma prevalence but only average per capita antibiotic use.

## Discussion

Research to date on antibiotic use early in life and subsequent risk of asthma has yielded conflicting results. One of the first reports was that of Farooqi *et al.*<sup>19</sup> who found significant associations between treatment with oral antibiotics in the first 2 years of life and subsequent asthma (odds ratio [OR] = 3.2), hay fever (OR = 2.0), and eczema (OR = 2.0) at age 12–20 years in Oxfordshire. The association was stronger for infections treated with broad spectrum antibiotics, and increased with the number of antibiotic courses received. Wickens *et al.*<sup>20</sup> reported that antibiotic use in infancy was a significant risk factor for 'asthma ever' (OR = 2.7) and 'wheeze ever' (OR = 1.9), but not for current wheeze (OR = 1.1) in children aged 5–10 years at Rudolf Steiner schools in New Zealand. Similarly, Alm *et al.*<sup>21</sup> found a lower prevalence of atopy in 5–13 year old school children from two anthroposophic (Steiner) schools compared with children in neighbouring schools. Droste *et al.*<sup>22</sup> found that the use of antibiotics during the first year of life was associated with an increased risk of asthma (OR = 1.7), hay fever (OR = 2.3), and eczema (OR = 1.3), but not atopy (OR = 1.1) in children aged 7–8 years in Antwerp. The associations with asthma, hay fever, and eczema were stronger in children with a parental history of hay fever, and were stronger with broad spectrum than with narrow spectrum antibiotics. However, the effect was stronger during the first half of the follow-up time than during the second half, a finding that the authors concluded was more in keeping with a bias due to reverse causation. McKeever *et al.*<sup>23</sup>

found no clear protective effects of personal or siblings' infections on the incidence of allergic disease in children in the West Midlands (UK); antibiotic exposure in early life was associated with an increased risk of asthma diagnosis but the association was reduced when the data were adjusted for consulting behaviour (relative risk [RR] = 2.0). The same group, using the same database in a different study,<sup>24</sup> investigated a number of prenatal exposures on the incidence of asthma, eczema, and hay fever and concluded that exposure to antibiotics *in utero* is associated with a dose-related increase in the child's risk of asthma (RR = 1.7), hay fever (RR = 1.6), and eczema (RR = 1.2), as well as similar though smaller effects for exposure to infections. These findings are consistent with an earlier study which demonstrated associations between infections in general in the first trimester of pregnancy with an increased risk of allergic disease.<sup>25</sup> On the other hand, Celedon *et al.*<sup>26</sup> found no significant association between antibiotic use in the first year of life and the subsequent development of asthma, allergic rhinitis, or eczema at age 5 years (OR for one versus no course of antibiotics, 0.7 [95% CI: 0.4, 1.4]; OR for two or more versus no course of antibiotics, 0.9 [95% CI: 0.5, 1.5]). Finally, Wjst *et al.*<sup>27</sup> found an association of antibiotic use with asthma diagnosis (one course OR = 1.9, 2–5 courses OR = 3.0,  $\geq 6$  courses OR = 6.9) in children aged 5–14 years in East Germany. However, the authors suggested that their findings may be due to reverse causation in that frequent upper respiratory infections, often an early symptom of asthma, are usually treated with antibiotics.

In our analyses, we found that there were positive associations between per capita antibiotics sales and the prevalence of symptoms for asthma, rhinitis, and eczema, but the associations generally became negative once the analyses had been adjusted for GNP. In particular, there were non-significant negative associations between total antibiotics sales and the prevalence of wheeze ever, wheeze in the last 12 months, nose problems with itchy-watery eyes, itchy rash in the last 12 months, and eczema ever. On the other hand there were non-significant positive associations for asthma ever, nose problems ever, nose problems in the last 12 months, and itchy rash ever.

Overall, the associations, as well as being non-statistically significant, are not strong. For example, the strongest positive association was for wheeze at rest as measured by the asthma video questionnaire. Even for this association, a one-unit increase in per capita antibiotic sales was only associated with an increase in asthma prevalence of 0.35%. Thus, even a doubling of the average antibiotic prescribing in the countries included in the study (from 3.3 to 6.6 per year) would only represent an approximately 1% increase in asthma prevalence. Furthermore, the finding for the asthma video questionnaire was based on only 61 centres and was different from the findings for the questionnaire analyses which were based on 99 centres. The written questionnaire analyses showed no statistically significant associations, and most of the observed associations were non-significantly negative.

Before considering these findings further, it is necessary to consider potential sources of bias. One key consideration is the accuracy of the data on which the calculations were based. Even though the antibiotics sales data are likely to be relatively accurate, they represent per capita sales for the total population, and there are no specific data available for sales for infants and

young children. The data used for the prevalence of asthma, allergic rhinoconjunctivitis, and atopic eczema were derived from the recently published ISAAC study which employed standardized methodology including both written and video questionnaires.<sup>30–34</sup> The asthma video questionnaire was designed to provide more accurate recognition of clinical asthma, and to avoid problems of translation of terms such as 'wheeze'. Furthermore, both written and video questionnaires have been validated using objective measures of traits closely associated with asthma such as atopic sensitization and airway hyperresponsiveness.<sup>30</sup>

It should also be noted that the antibiotics sales data were available at the country level, whereas the symptom prevalence data were collected in multiple centres for each country. We performed a simple weighted linear regression for ease of interpretation; if a mixed model regression had been conducted to incorporate the different structure of the data sets, then the effect estimates would not have changed, but the standard errors would have increased and the *P*-values would have been higher. Therefore the findings would not have changed markedly since, with one exception, we found no statistically significant associations even using the simple linear regression analyses. This is in contrast to some other ecologic analyses of the ISAAC data,<sup>36–40</sup> including the statistically significant negative association of tuberculosis notification rates and asthma symptom prevalence.<sup>36</sup> Thus, it appears unlikely that the lack of statistically significant findings in the current analyses was due to methodological issues alone.

In summary, these findings are generally not consistent with the hypothesis that antibiotic use increases the risk of asthma, rhinitis, or eczema. It should be stressed that these analyses do not involve information on individual antibiotic exposures and

therefore do not refute the hypothesis that, at least in some circumstances, antibiotic exposure early in life may increase the subsequent risk of developing asthma. However, these analyses do indicate that this association, even if it is causal, does not account for the international differences in asthma prevalence, and that other risk factors for asthma must account for the observed international patterns.

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### KEY MESSAGES

- An ecologic analysis has been conducted of antibiotics sales and the prevalence of symptoms of asthma, rhinitis, and eczema in children in 99 centres from 28 countries.
- There were positive associations of antibiotics sales with symptom prevalence but these generally became negative when the analyses were adjusted for gross national product.
- These findings are generally not consistent with the hypothesis that antibiotic use increases the risk of asthma, rhinitis, or eczema.
- If there is a causal association of antibiotic use with asthma risk it does not appear to explain the international differences in asthma prevalence.

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