Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Adverse ecological effects on the individual as a consequence of previous antibiotic exposure

A systematic review

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ISBN 978-91-7603-266-4 (pdf)
ISBN 978-91-7603-267-1 (print)

Preface in Swedish

Antibiotika är viktiga läkemedel och en förutsättning för modern sjukvård. Samtidigt finns besvärliga bieffekter av användningen av antibiotika, och den viktigaste är selektion av resistenta bakterier. Detta är väl dokumenterat i både stora epidemiologiska studier och laboratorieexperiment. Däremot är det mer sällan risken för framtida resistens är en fråga som spelar roll i mötet mellan patient och läkare. Istället ligger fokus på om användningen av antibiotika i den specifika situationen medför större nytta än de eventuella biverkningarna.

Vi har undersökt om det finns några dokumenterade ekologiska biverkningar av antibiotikaanvändning på individnivå. Direkta organtoxiska effekter av antibiotika liksom allergiska reaktioner av läkemedlen är dock ganska väl beskrivna tidigare och berörs därför inte närmare i den här rapporten.

Rapporten är tänkt att användas av lokala Stramagrupper, läkemedelskommittéer och enskilda vårdgivare i arbetet med rationell antibiotikaanvändning.

Rapporten är skriven på engelska av Jessica Tikkala med handledning av Anders Ternhag, överläkare på Folkhälsomyndigheten. Rapporten är ett studentarbete på Läkarprogrammet i Örebro.

Folkhälsomyndigheten

Malin Grape
Enhetschef Antibiotika och vårdhygien

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Swedish summary

Antibiotika ökar risken för sekundära infektioner med resistenta bakterier

Tvärtemot vad många tror smittas man inte alltid av bakteriella infektioner när man blir sjuk. Många infektioner orsakas istället av att bakterier man är koloniserad med får övertag, växer till och kan spridas till en lokal där de normalt inte finns. Det humana mikrobiomet utgörs av ungefär 10^{14} bakterier som lever framförallt i tarmen. Ett problem med antibiotika är att de inte kan skilja mellan sjukdomsalstrande bakterier och bakterierna i mikrobiomet. Det tar också flera veckor efter en antibiotikakur innan mikrobiomet börjar normaliseras igen.

Vi har gjort en systematisk genomgång av den vetenskapliga litteraturen om vilka negativa ekologiska effekter antibiotika kan ha på individnivå. Från början identifierades 535 artiklar där vi genom att läsa titlar och abstracts valde ut och läste 61 artiklar. Av dessa valde vi sedan ut 36 artiklar som inkluderades i den här systematiska översikten. Artiklarna grupperades i fem olika sjukdomsområden utifrån tänkbara negativa effekter av antibiotikaexponering: sekundära infektioner, inflammatorisk tarmsjukdom och irritabel tarm, astma och allergi, obesitas samt cancer.

Sammanfattningsvis finns det stöd för att antibiotikabehandling ökar risken att efteråt drabbas av andra infektioner orsakade av mer resistenta bakterier än vad som annars skulle vara fallet. Det vill säga, antibiotikaexponering selekterar fram resistenta bakterier som inte bara koloniserar värden utan också kan orsaka infektion. Det finns däremot inte tillräckligt med underlag för att säga att antibiotika har andra ekologiska biverkningar på individen. Direkta organtoxiska effekter och allergiska biverkningar av antibiotika omfattas dock inte av den här rapporten.

Summary

Objective: To review and summarize recent studies concerning the adverse ecological effects of antibiotics on the commensal microflora of exposed individuals and the accompanying secondary diseases.

Materials and Methods: The PubMed database was systematically searched for studies published between 2009 and 2013 using the following three search phrases: "individual risk of antibiotic exposure", "collateral damage and antibiotics", and "adverse ecological effects of antimicrobial agents". Studies concerned with antibiotic side effects caused by collateral damage with direct effects on the individual exposed to antibiotics were included. Excluded were articles not addressing humans, those written in a language other than English, and those describing toxic and allergic side effects or pharmacological interactions. A total of 36 articles were included and were grouped into the following five groups: "Secondary infection", Inflammatory bowel disease/Irritable bowel syndrome", "Asthma, allergy, eczema, and rhinitis", "Obesity", and "Cancer".

Results: Antibiotic therapy was found to be a risk factor for various subsequent secondary infections, i.e. infections with other bacteria than the initial infection. These infections include bloodstream infections, urinary tract infections, gastro-intestinal infections, and – in the case of neonates – necrotizing enterocolitis. Antibiotic use in early childhood showed a weak association with asthma, although the aetiology of asthma is complex where several described environmental exposures interact with genetic inheritance to the risk for disease. No clear relationship was seen between antibiotic exposure and food allergies. The articles investigating the relationship between antibiotics and inflammatory bowel disease showed a different pattern for Crohn's disease and ulcerative colitis with a correlation only between antibiotics and Crohn's disease. It is unknown whether this reflects a shared susceptibility to infections and Crohn's disease or if antibiotic exposure is a factor in disease development or if the findings are due to bias. An association between prior antibiotic therapy and obesity and cancer was also studied in a few of the articles obtained from the literature search. However, these studies show conflicting or insignificant results, and a causal relationship is unlikely.

Conclusions: The collateral damage associated with antibiotic exposure is a risk factor for subsequent secondary infections, and the antibiotic itself can have a negative impact on the individual patient due to its effect on the commensal microflora. Thus, in the treatment of bacterial infections, at least the less severe ones, the ecological side effects are important factors to keep in mind for the prescribing clinician.

Introduction

Antibacterial agents are frequently used to treat various bacterial infections in humans. Like all drugs, antibiotics have side effects that have to be taken into consideration before and during therapy. For antibiotic agents, perhaps the most well known are toxic and allergic side effects and pharmacologic interactions (1). However, because of the remarkably large and complex colonies of commensal bacteria in different parts of the human body there are also less obvious adverse effects of antibiotic use that might not always be as direct. These adverse ecological effects are often referred to as collateral damage (2).

The human microbiota consists of approximately 10^{14} bacterial cells, which is 10 times greater than the total number of human cells in one individual (3). The largest and most complex population is present in the human gastrointestinal tract, and studies on faecal samples have revealed the presence of between 1000 and 1150 different bacterial species (3). This population has been implicated in playing a role in human nutrition, immune system maturation, homeostasis, and in resisting colonization by pathogenic bacteria (1). The make-up of the human commensal flora can shift as a consequence of antibiotic use, especially after repeated treatments (4). Antimicrobials are not able to target their effects on individual pathogens or specific body parts, and they invariably affect the body microflora as a whole (2). It is well known that antibiotic use can perturb the commensal microflora, sometimes permanently (4), but the implications of this shift in commensal microflora are poorly understood.

Perhaps the best-known consequences of collateral damage is the antibiotic-associated diarrhoea caused by *Clostridium difficile* or the overgrowth of *Candida albicans* (5), both of which are direct effects of antibiotic use and, therefore, easy to link to exposure to antibiotics. Bearing in mind the known functions of the commensal flora on nutrition, immune system maturation, and homeostasis, it is possible that there are additional consequences of a disturbance of the normal flora, including more long-term effects.

The objective of this study is to review the literature concerning the adverse ecological effects of antibiotics on the exposed individual.

Materials and methods

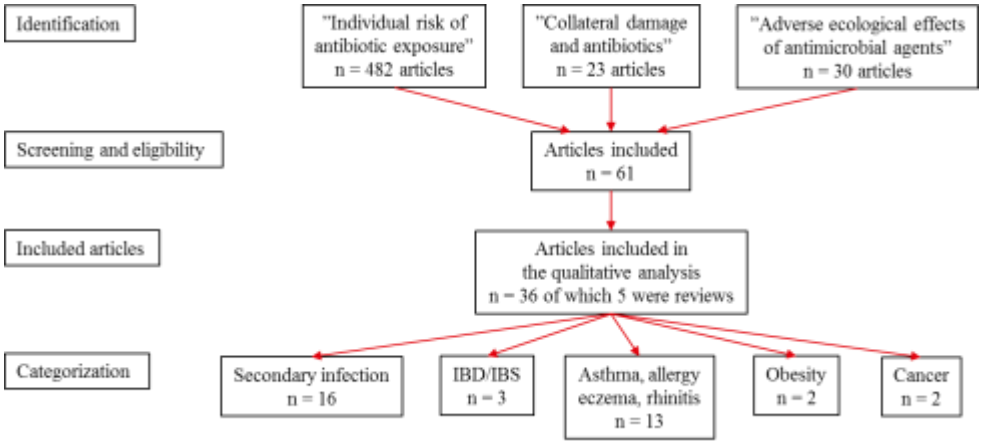
The PubMed database (www.ncbi.nlm.nih.gov/pubmed) was searched for articles restricted to the last five years (2009–2013). The PICO method (Patient, Intervention, Comparison, and Outcome) of strategic database searching was not applicable in this case because the outcome was not known. Similarly, conducting a search strictly using MESH terms proved to be unfruitful due to the large number of articles generated by this kind of search. Therefore, three specific search phrases were used including "individual risk of antibiotic exposure", "collateral damage and antibiotics", and "adverse ecological effects of antimicrobial agents".

Due to the broad nature of the search, the articles were screened with specific inclusion and exclusion criteria by means of title and abstract analysis. The inclusion criterion was articles concerned with the adverse effects of antibiotics that were caused by ecological effects involving perturbation of the normal microflora. Exclusion criteria included studies on toxic adverse or allergic effects, pharmacological interactions, and antifungal or antiviral pharmaceuticals. In vitro and purely ecological studies were also excluded. Resistance development was not included on a larger scale, and only individual consequences on the exposed person were considered. We also limited the articles by excluding those discussing colonization, but not infection, with pathogenic bacteria. Finally, articles older than five years, those not written in English, and those involving subjects other than humans were also excluded.

Results

The PubMed search resulted in 535 articles that were screened for eligibility based on their titles and abstracts. Of these, 61 articles were selected for a more thorough reading. This reading resulted in 36 included articles, of which 16 were classified in the Secondary infection group; 3 in the Inflammatory bowel disease/Irritable bowel syndrome (IBD/IBS) group; 13 in the Asthma, allergy, eczema, and rhinitis group; 2 in the Obesity group; and 2 in the Cancer group.

Figure 1. Flow chart illustrating the search methodology.



Secondary infections

Bacterial infection or the risk of infection is the primary reason for prescribing antimicrobials, but the collateral damage of such agents might also cause infection by selecting for pathogenic bacteria. In a review from 2011, Stewardson et al. presented data supporting the theory that antibiotic exposure is a risk factor for subsequent colonisation and infection by both gram-positive and gram-negative pathogenic bacteria (1).

Ginn et al. evaluated intensive care patients who were treated with alternating cefepime and antipseudomonal penicillin/beta-lactamase inhibitor combination (APP-β) in four-month cycles and its microbiological outcomes in terms of the presence of antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* (6). They found that overall mortality and antibiotic resistance was unchanged after 16 months of treatment. However, during cefepime cycles infection by antibiotic-resistant bacteria was observed, but these levels of infection returned to baseline during the APP-β cycles.

Vellinga et al. studied the risk of trimethoprim and ciprofloxacin resistance in treating *Escherichia coli* urinary tract infections (7). Their study suggested that the likelihood of the *E. coli* infection becoming resistant to antibiotics increases with an increasing number of prescriptions in the previous year. The odds ratio (OR) and 95% confidence interval (CI) that the bacteria were resistant to ciprofloxacin was 2.7 (1.2–5.6) for one prescription in the previous year and 6.5 (2.9–14.8) for

two or more prescriptions. For trimethoprim, the OR and 95% CI of the bacteria being resistant to the drug was 4.7 (1.9–12.4) after at least two prescriptions and 6.4 (2.0–25.4) for three or more prescriptions.

Other *E. coli*-specific studies investigated risk factors for bloodstream infections caused by extended spectrum beta lactamase (ESBL)-producing and non-ESBL-producing *E. coli* (8-10). In addition, risk factors associated with carbapenem-resistant *Enterobacteriaceae* were studied (11). The two studies focusing on the ESBL production of the bacteria found a significant association between prior antibiotic use and ESBL production (9, 10). Wu et al. found the highest association with ESBL production when oxyimino-cephalosporin (not specified) had been used (OR 5.16 (95% CI 1.03–25.79)) (10).

Carbapenem resistance was studied by Kritsotakis et al. for ESBL-producing *Klebsiella pneumoniae* infection (12). A statistically significant relationship was shown for previous exposure to carbapenems, beta-lactam/beta-lactamase inhibitor combinations, and fluoroquinolones. A significant interaction effect was also shown for carbapenems and fluoroquinolones.

Freeman et al. also investigated the risk factors associated with ESBL bacteraemia, but with a focus on the *Enterobacteriaceae* as a group (13). This study, however, found exposures to first-generation cephalosporins and fluoroquinolones to be independent risk factors for ESBL-*Enterobacteriaceae* bacteraemia. Known colonisation with an ESBL-*Enterobacteriaceae* was also an independent risk factor. The study furthermore showed that ESBL-*Enterobacteriaceae*-associated bacteraemia had a worse prognosis and higher mortality compared to the controls with non-ESBL bacteraemia.

Chang et al. also studied *E. coli* bacteraemia with a focus on carbapenem resistance related to risk factors such as prior antibiotic exposure (8). Due to its importance as a treatment for multidrug-resistant gram-negative pathogens, carbapenem resistance constitutes a serious medical issue, and bacteraemia caused by the pathogen often leads to a worse outcome for the patient. Cases of carbapenem-resistant bacteraemia were matched with carbapenem-susceptible strains and antibiotic exposure, and previous carbapenem exposure was found to be more frequently observed in patients with non-susceptible diseases.

A study by López-Dupla et al. investigated the risk factors associated with antibiotic-resistant *P. aeruginosa* bacteraemia (14). The antimicrobial risk factors studied were exposures to previous antipseudomonal antibiotics. Exposure to ciprofloxacin within the past 30 days was associated with ciprofloxacin, ceftazidime, imipenem, meropenem, and piperacillin-tazobactam resistance, including multidrug resistance, in subsequent *P. aeruginosa* bacteraemia. These authors found a predisposition to stronger resistance to imipenem and ciprofloxacin if these antibiotics had been used previously. Ceftazidime, meropenem, and piperacillin-tazobactam, however, did not predispose to resistance to themselves. In addition, meropenem and piperacillin-tazobactam did not predispose to cross-resistance with any of the other antibiotics assessed in the study.

Previous systemic antibiotics are a well-defined risk factor for bloodstream infection with *Candida sp*. Candidaemia is associated with higher mortality, longer hospital stay, and excessive costs, and in recent years there has been a shift in the distribution of *Candida sp*. that cause invasive infection to an increase in non-*albicans* species (15). Particular concern has risen from fluconazole-resistant *Candida glabrata* and inherently fluconazole-resistant *Candida krusei*. A study by Ben-Ami et al. investigated the association of antibiotic exposure with the risk for fluconazole-resistant *Candida sp*. bloodstream infection (15). A positive association was found between *C. glabrata* infection and metronidazole exposure and a negative association with aminoglycoside exposure. For the fluconazole-resistant *Candida sp.* bloodstream infections, a positive association was found for trimetoprim-sulfamethoxazole, carbapenems, clindamycin, and colistin. Exposure to cephalosporins was negatively associated with infection.

The relationship between previous antibiotic exposure and campylobacteriosis was studied by Koningstein et al. (16). In addition, resistance to fluoroquinolones and macrolides was assessed. The study was a register-based case-control study on 31,669 laboratory-confirmed cases of campylobacteriosis between 1999 and 2005 in Denmark. Increased exposure to fluoroquinolones, macrolides, sulphonamides, trimethoprim, tetracyclines, and broad- spectrum penicillins up to 1 year before the onset of disease was positively correlated with campylobacteriosis. The highest association was found for fluoroquinolones, and the risk was also higher for infection by resistant isolates than for susceptible ones.

Two of the articles from the literature search investigated the well-established risk of a *C. difficile* infection (CDI) after exposure to antibiotics. Hensgens et al. focused on the time interval between exposure and infection (17), and Stevens et al. assessed the degree to which cumulative antibiotic exposure over time was associated with a CDI (18). *C. difficile*-associated diarrhoea is a highly variable infection with symptoms ranging from mild diarrhoea to severe pseudomembranous colitis. Mortality varies depending on virulence from 6% in endemic cases to 17% when the hypervirulent form is involved (17). In earlier studies, most classes of antibiotics have been associated with the risk of CDI. Hensgrens et al. studied the time interval for infection and found that during antibiotic therapy and in the first month after cessation patients had a 7-fold to 10-fold increased risk for CDI. At 3 months after antibiotic therapy, the risk had declined. In this study, all antibiotic classes except first-generation cephalosporins and macrolides were associated with CDI. The strongest correlation was seen with second- and third-generation cephalosporins and carbapenems. Neuberger et al. also studied CDI in travellers and found that CDI in travellers usually occurs in relatively young patients (19). The empiric use of antibacterial agents has frequently been associated with CDI, especially fluoroquinolone. Stevens et al. examined the total dose, duration, and number of antibiotics – i.e. the cumulative risk of antibiotic exposure – with the risk of CDI (18). In this study, patients who received two antibiotics had a 2.5-fold increased risk of infection when compared with the patients only treated with one antibiotic. The risk increased to 3.3 and 9.6

when the patient received 3 or 4 antibiotics or 5 antibiotics, respectively. The same pattern was observed for cumulative dose and duration of antibiotic exposure.

Risk factors for healthcare-associated pneumonia were studied by Poch et al (20). Healthcare-associated pneumonia, a category of nosocomial pneumonia, includes patients who have been hospitalized in an acute care hospital for 2 or more days within the past 90 days; residents of nursing homes or long-term care facilities; recipients of intravenous antibiotic therapy, chemotherapy, wound care, or chronic dialysis within the past 30 days. Antibiotic use was one of many risk factors addressed, and antibiotic use was found to be a strong risk factor for infection with drug-resistant organisms in these patients.

Preterm neonates are another vulnerable group of patients because of the lack of microbial diversity in their intestinal flora compared to adults. They have fewer *Bifidobacterium* and *Lactobacillus* and are at greater risk of being colonised with *E. coli*, *Enterococcus sp*., and *K. pneumonia* (21). The proliferation of these organisms can invade the intestinal wall and cause an inflammatory reaction. The case-control study by Alexander et al. was designed to determine if the duration of antibiotic exposure was an independent risk factor for necrotizing enterocolitis (21). This was found to be true among neonates without prior sepsis, and the risk of necrotizing enterocolitis steadily increased as the duration of cumulative antibiotic exposure increased. The cohort with sepsis, however, had a decreased risk of necrotizing enterocolitis as the cumulative duration of antibiotic therapy increased.

Inflammatory bowel disease (IBD) and Irritable bowel syndrome (IBS)

The correlation between prior antibiotic use and the incidence of IBD has also been studied. In a Finnish register-based study from 2012, the authors followed children born between 1994 and 2008 who had been diagnosed with IBD by October 2010. Their study included 595 children with IBD and 2,380 matched controls (22). In the IBD group, 233 were diagnosed with Crohn's disease and 362 with ulcerative colitis. Almost all of the children in the study had been exposed to at least one antibiotic between time of birth and index date, and there was no significant difference in antibiotic exposure between the IBD and the control group. The overall use of antibiotics was more frequent in the Crohn's disease group compared to the controls, but no significant difference could be established between the ulcerative colitis group and the controls. The overall use of antibiotics was significantly associated with Crohn's disease even after exclusion of exposure to antibiotics during any of the 6 months preceding diagnosis of the case. The association was significantly stronger for boys than for girls. An increasing number of prescription antibiotic purchases was also associated with Crohn's disease but not ulcerative colitis. The risk was highest for 7–10 purchases and did not increase with additional purchases. Cephalosporins had the strongest association to Crohn's disease. The authors discuss whether the association between antibiotic exposure

and Crohn's disease reflect a shared susceptibility to childhood infections and Crohn's disease or if exposure could trigger disease development.

The review article by Ng et al. investigated the geographical variability and environmental risk factors for IBD (23). One risk factor assessed was prior antibiotic exposure, and they concluded that the observational studies showed an association between antibiotic use and IBD regardless of whether the antibiotics were taken in infancy, childhood, or at another point before IBD diagnosis. The authors, however, were uncertain whether the relationship is causal. It has been hypothesised that antibiotics cause an imbalance in the microbiota of the gut and thus affect the gut immune tolerance, which favours IBD onset, but antibiotic use could also be a marker for the presence of infectious processes leading to IBD.

The association between broad-spectrum antibiotic exposure and IBS was studied in a retrospective American study (24). A total of 21,364 patients were included in the study and 115 patients (0.54%) developed IBS. The study concluded that there might be an association between IBS and broad-spectrum antibiotics, particularly macrolides and tetracyclines. The authors discussed possible mechanisms for this correlation and hypothesised about whether bacterial or *Candida* overgrowth are possible explanations.

Asthma, Allergy, Eczema, and Rhinitis

Asthma and allergic diseases are common chronic diseases of childhood, and numerous studies in different countries have indicated that the prevalence of these diseases have increased significantly over the last decades (25, 26). Antibiotics are commonly used as treatment for infections during childhood, and their use in children has increased along with the increase in asthma and allergies (26). This observation corresponds well with the "hygiene hypothesis". This states that growing up in a more hygienic environment with less microbial exposure might interfere with the normal development of the immune system and the shift from T helper cell 2 (Th2) response to Th1 response and that this makes the individual more prone to Th2, or atopic, immune responses (26). Several studies, both prospective and retrospective, have explored the association between antibiotic exposure and the development of asthma, allergies, eczema, and/or rhinitis (25-36). Some articles also explored the risk of asthma or allergies in children as a consequence of antibiotic use by the mother during pregnancy (27, 35).

Almost all of the studies concluded that antibiotics slightly increase the risk of childhood asthma (25, 31, 32, 34-36). Murk et al. presented a number to harm of 87; that is, for every 87 children exposed to antibiotics, one child will develop asthma assuming a baseline childhood asthma incidence rate of 10% (31). However, the authors discussed the difficulty with possible reverse causality, or protopathic bias, in these kinds of studies. Indication bias, which occurs when an independent risk factor like respiratory infection is treated with an antibiotic, is also a problem. Recall bias is another relevant confounder considering the relatively higher pooled risk for asthma in retrospective studies compared to

database and prospective studies. In several of the studies, protopathic bias was depressed by lengthening the time between exposure (antibiotics) and outcome (asthma) (31, 32). Indication bias was also pared down by adjusting for respiratory infections and other known confounders (25, 31, 32, 35).

Murk et al. also reported a great variety in the types of antibiotic previously reported to be associated with the risk of asthma (31). McKeever reported amoxicillin, macrolides, cephalosporins, and sulphonamides, but not penicillins, to be associated with a relatively high risk of asthma, but Marra et al. reported that penicillins were also associated with a relatively high risk (31). Other studies have divided the antibiotics into broad-spectrum versus narrow-spectrum and found a higher OR for the broad-spectrum antibiotics and asthma (25). Jedrychowski et al. stated in their study that an excess of wheezing episodes was only related to macrolides, and this suggests that macrolides have a stronger proallergic effect (25).

Some studies have also assessed the cumulative effects of antibiotic use and found that as the numbers of antibiotic courses increases, the risk of asthma also increases (26, 32). The risk seems to be highest in children who receive more than four courses, and the increased risk for asthma is associated with all antibiotics except sulphonamides (26). In a study by Risnes et al., the adverse effect of antibiotics in the form of asthma was particularly strong in children with no family history of the disease (32). Murk et al., however, found no statistical difference when comparing these two groups (31).

In addition to the studies mentioned above, Sobko et al. investigated the hypothesised protective effect of neonatal sepsis on the risk for later asthma (34). They found that neonatal sepsis was actually a risk factor for later asthma and that neonatal sepsis with *Streptococci* is also associated with atopic eczema. The same study also had a cohort who had received antibiotics for prophylactic reasons without infection. The cohort with both sepsis and antibiotic treatment and the cohort with only antibiotic exposure had the same direction of association with asthma, and this led the authors to suggest that asthma in both cohorts could be due to neonatal exposure to antibiotics.

Exposure to antibiotics by pregnant women and the incidence of asthma in their children has been evaluated, and these studies have also found a similar association between antibiotic exposure and asthma (35). However the possibility of confounders in these studies is significant even after adjustments for prematurity, chorioamnionitis, and maternal smoking. The Danish study by Stensballe et al. found no evidence for certain types of antibiotics to increase the risk for asthma, but their study was not fully powered for subgroup analysis (35). In addition to this, no evidence was found for a relationship between antibiotic exposure in the mother and subsequent eczema in the child.

Eczema, the most common chronic childhood disease with a prevalence of 11% in preschool children, has also been studied as an outcome of previous antibiotic exposure (33). Schmitt et al. investigated both infection and antibiotics as risk

factors and found that antibiotic exposure during the first year of life increased the risk of atopic eczema during the second year (33). The relationship was dose dependent, and children receiving two or more courses of antibiotics had a more than twofold risk of developing atopic eczema. The risk differed, however, depending on antibiotic class, with no altering effect for penicillins but a positive association for macrolides and cephalosporins. No association between antibiotic exposure and allergic asthma was found in this study, but there was an increased risk of eczema following infection. This relationship was modified, however, by antibiotic treatment. When not treated with antibiotics, infections were generally not found to be significantly associated with atopic eczema. While children with early respiratory tract infections not treated with antibiotics had a non-significant protective effect from the infection, the children receiving macrolides (relative risk (RR) 2.15, 95% CI 1.18–3.49) or cephalosporins (RR 1.93, 95% CI 1.07–3.49) had a significantly increased risk of atopic eczema (33). The study by Dom et al. found that antibiotic exposure both before and after the first year appears to be protective against allergic symptoms (27). However, exposure in utero or during lactation was more strongly associated with risk for allergic symptoms in the form of eczema for prenatal exposure and in the form of wheeze for lactation exposure.

Food allergy is another common atopic manifestation among children, and allergies to nuts, milk, and egg are the most common. The EuroPrevall birth cohort study on food allergies examined the regional differences in prevalence and risk factors of food allergies in Europe (37). Significant differences were found in the prevalence of allergies in both children and parents as well as several risk factors, including antibiotic use. Two other studies also investigated the risk factors for food allergies. Dowhower Karpa et al. investigated risk factors for IgE-mediated food allergies as a whole (28), and Koplin et al. looked specifically at the risk factors for egg allergy (30). The antibiotic exposures were perinatal in the study by Dowhower Karpa et al. and during the first year in the Koplin study. Both studies were unable to find an association between previous use of antibiotics and food allergies.

Allergic rhinitis and its relationship to antibiotic exposure was investigated in only one study (29). This Korean study investigated environmental risk factors and their interactions with genotype in elementary school children and found that taking antibiotics for more than 3 days during infancy was an independent risk factor for allergic rhinitis.

Obesity

The 2011 Danish longitudinal and prospective study by Ajslev et al. investigated several risk factors for obesity at 7 years of age (38). One factor was early exposure to antibiotics, and the cut-off was set at antibiotic use before the age of 6 months. This exposure was found to increase the OR for childhood obesity, but the association did not persist when adjusting for covariates. However, when the mothers were categorised into groups according to maternal pre-pregnancy body mass index (BMI), the group observed an increased risk for childhood obesity in

antibiotic-exposed children born to normal-weight mothers. An inverse relationship was observed in the children of overweight mothers where antibiotics had a small protective effect. The increased risk of obesity was observed for both girls and boys of normal-weight mothers, but after adjusting for maternal age, smoking, socioeconomic status, birth weight, and breastfeeding the increased risk only persisted for boys. The authors of the study hypothesised on the explanation for this effect and suggested that the widely accepted use of antibiotics as growth-promoting ingredients in animal feed might have a similar effect in humans (38). It has been reported that the oral use of antibiotics in the first months of life results in decreased numbers of *Bifidobacteria* and *Bacteroides fragilis* group species, and *Bifidobacteria* have been reported to be more prevalent in lean subjects.

Trasande et al. also studied the risk for obesity at age 7 in a longitudinal birth cohort study (39). However, this study considered antibiotic exposure up to 2 years of age and divided this period into three distinct ages (<6 months, 6–14 months, and 15–23 months). The group reported that the composition of the microbiota in adults appears to be relatively stable according to recent studies on the human microbiome. However, the microbiota in children might be considerably more variable and vulnerable, especially to the perturbations caused by antimicrobial agents. This study also showed a correlation between antibiotic exposure at <6 months and increasing BMI and obesity from ages 10 months to 38 months. However, this relationship did not persist to 7 years of age. Later exposure at the age of 15–23 months showed a significant correlation with elevations in BMI at the age of 7, but this relationship did not persist when adjusting for potential confounders (39).

Cancer

Two articles in our literature search investigated the association between antibiotic exposure and cancer. Both studies were population-based case-control studies using data from the Saskatchewan Health Administrative databases in Canada and were conducted partly by the same research group. The first study assessed the risk of prostate cancer (40) and the second assessed the risk of gynaecological cancers (cervical, ovarian, and uterine cancers) (41). In both articles, the authors referred to earlier studies in the field and especially studies concerned with the relationship between antibiotic exposure and breast cancer in which conflicting results have been reported. Where a positive correlation between antibiotics and cancer was found the mechanism was speculative, and the fact that most studies found similar increases in the risk of breast cancer across the different antibiotic classes speaks for a less likely causal effect. Thus, confounding factors could affect the observations, and chronic inflammation has been suggested as one confounder associated with both infection and breast cancer. However, in the study by Tamim et al., which focused on gynaecological cancers, no correlation was found between antibiotic exposure and ovarian or uterine cancers (41). In the case of cervical cancer, the group found that exposure to antibiotics from 1 year to 15 years prior to the cancer diagnosis reduced the cancer risk significantly. In the study on the risk

of prostate cancer after antibiotic exposure, however, a dose-dependent association was found (40). Due to the lack of temporal trends, the timing of the association, and the absence of antibiotic class-specific effects, the authors concluded that the associations in both of the articles was probably non-causal.

Discussion and conclusions

We have conducted a systematic review of adverse ecological effects of antibiotic exposure at the individual level. The most important finding is that antibiotics appear to increase the risk of secondary infections with bacteria other than those of the initial infection, and these secondary infections are often associated with troublesome resistance patterns. These infections include bloodstream infections, urinary tract infections, gastro-intestinal infections, and, in the case of neonates, necrotizing enterocolitis.

This is to our knowledge the first comprehensive review of the various possible non-toxic or directly allergic outcomes of previous antibiotic exposure that are not limited to short- or long-term effects or type-specific outcomes such as exclusively secondary infections or atopic manifestations. The study's limitations are related to the extent of the study, and there is a risk of not having found all the relevant articles and outcomes.

Most of the studies included in this review are various epidemiological studies. This is because antibiotics are common drugs, and more severe ecological side effects seem to be rare making randomized clinical trials difficult to perform. The inherent problems with selection bias and confounding in epidemiological studies (compared to randomized clinical trials) are, therefore, valid for most of the included studies.

A five-year limitation in the literature search was applied due to time constraints in analysing the material, and this could have had some effect on the results. Another limitation is that for many of the epidemiological associations, the biological mechanism is unknown and this makes causal relationships difficult to determine.

Two articles derived from the search examined the relationship between previous antibiotic exposure and IBD (22, 23), and another study examined the association to IBS (24). These studies found a possible association between previous antibiotic use and Crohn's disease, and the association was stronger with cumulative use, especially for cephalosporins. A similar relationship was not found for ulcerative colitis. The study examining the relationship between broad-spectrum antibiotics and IBS found that there might be a relationship, especially for macrolides and tetracyclines.

These studies are difficult to evaluate, however, because of several possible confounders. Reverse causality (or protopathic bias) is one possibility. In this case, the reasons for antibiotic use are early symptoms of IBD or IBS that has not been diagnosed yet. It is, however, interesting to note the difference in association with Crohn's disease and ulcerative colitis, which suggests different disease mechanisms. For any significant conclusion to be made, however, more research in this area is required.

The studies investigating the association between antibiotic exposure and asthma seem to point in the direction that a weak correlation exists (25, 26, 31, 32, 34).

Some studies also seem to imply that this association is stronger for broad-spectrum antibiotics and for cumulative exposure as well as for children without a family history of asthma (25, 32). Although these findings suggest a weak correlation one must remember that the cause of asthma is complex with several described environmental risk factors (e.g. allergic sensitisation, passive tobacco smoking) which interact with genetic inheritance.

Prenatal exposure to antibiotics has similarly been associated with a slightly increased risk of asthma (35). The association between prenatal antibiotic exposure and asthma has been studied in parallel with postnatal exposure and asthma. However, because in utero life is sterile, it is unlikely that this association is due to an ecological perturbation in microflora. Therefore, even though the association pattern shows similar trends, the biological mechanisms most likely differ for prenatal and postnatal exposure provided that the mechanism for postnatal exposure is ecological.

A class-specific association between antibiotic exposure and eczema was found in the study by Schmitt et al. (33). Penicillins showed no association, but significant associations were observed for macrolides and cephalosporins. Antibiotic exposure and its relationship with food allergies was investigated in two of the articles, neither of which found a statistically significant relationship (28, 30). In a similar manner as the studies on IBS and IBD, these studies of different atopic diseases are at risk of confounders clouding the results. However, the risk of protopathic bias has been decreased in many of the studies by extending the time between exposure to the antibiotics and the outcome. Indication bias for the asthma studies was decreased by adjusting for respiratory infection and other known biases. However, there could be unknown biases considering that the disease mechanisms for these atopic diseases are still not well understood.

The association between antibiotic exposure in children and childhood obesity was studied in two articles (38, 39). Both found a small association for children born to normal-weight mothers, especially for boys. The increase in weight was small for the individual child and significant only for the cohort as a whole (39).

The two studies examining the relationship between antibiotics and cancer investigated prostatic cancer (40) and gynaecological cancers (41). For cervical cancer, previous antibiotic exposure was found to be protective, but for the other gynaecological cancers no association was found. The authors suggest that the relationship probably is non-causal. The opposite, or a small association, was found for antibiotics and prostate cancer, but due to the lack of any temporal trends and the absence of any antibiotic class-specific effects the authors found it unlikely to be a causal relationship. Previous studies on antibiotic exposure and breast cancer have also found conflicting results.

Antibiotic agents are valuable drugs that save lives, decrease morbidity, and enable much of modern medicine. However, there are side effects to antibiotics, just as there are for all drugs, and antibiotics stand out for having ecological side effects that still are largely unknown in addition to having toxic and allergic side-effects.

The benefits of a drug always have to outweigh the risks, and in the case of antibiotics it is important that the prescribing physician takes into consideration that there are possible individual negative effects caused by collateral damage to the commensal microflora.

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Appendix

Table 1. Articles included in this study with summaries of the study objectives and main findings.

Type of risk	Ref.	Objective, type of analysis	Main findings
Secondary infection	(5)	Use of cefepime vs. antipseudomonal penicillin/beta lactamase inhibitor combinations and the presence of antibiotic-resistant bacteria and/or methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in two metropolitan ICUs, Sydney and Brisbane, Australia	Cefepime cycles were associated with increased infection by antibiotic-resistant bacteria, but overall antibiotic resistance was unchanged after 16 months.
Secondary infection	(18)	Risk of *Clostridium difficile* infection (CDI) associated with total dose, duration, and number of antibiotics, retrospective cohort study among hospitalized adult patients, New York, USA	Cumulative antibiotic exposure appears to be associated with the risk of CDI.
Secondary infection	(12)	Identification of various antibiotics as risk factors for carbapenem-resistant ESBL-producing *Klebsiella pneumoniae* infection (ESBL-CRKP), case-case-control study, Heraklion, Greece.	ESBL-CRKP risk rose with increasing duration of prior beta-lactam/beta-lactamase inhibitor combinations. Increased fluoroquinolone treatment also amplified the impact of exposure to carbapenems.
Secondary infection	(14)	Risk of beta-lactam antibiotic resistance in subsequent *P. aeruginosa* bacteraemic isolates after ciprofloxacin exposure, case-control study, Tarragona and Barcelona, Spain	Exposure to ciprofloxacin during the 30 previous days was an independent risk factor for resistance to ceftazidime, imipenem, meropenen, piperacillin-tazobactam, ciprofloxacin, and multidrug resistance, with odd ratios varying from 2.5 to 3.95 for the different drugs.

Secondary infection	(8)	Risk factor analysis of carbapenem-nonsusceptible *Escherichia coli* bacteraemia, case-control study, Taoyuan, Taiwan	Prior exposure to carbapenems was an independent risk factor for carbapenem-nonsusceptible *E. coli* bacteraemia.
Secondary infection	(9)	Risk factors and mortality for community onset ESBL-producing and non-ESBL-producing *E. coli* bacteraemia, retrospective cohort study, Kaohsiung, Taiwan	Recent antibiotic exposure (within 30 days) was a significant risk factor for ESBL-producing *E. coli* bacteraemia.
Secondary infection	(10)	Risk factors for ESBL-producing *E. coli* bacteraemia, Taipei, Taiwan	Prior exposure to antibiotics, especially oxyimino-cephalosporins, are independent predictors of ESBL-producing *E. coli* bacteraemia.
Secondary infection	(17)	Determining the time interval between exposure to antibiotics and increased risk for CDI, case-control study, The Netherlands	All antibiotic classes except first-generation cephalosporins and macrolides were associated with CDI, with third generation cephalosporins and carbapenems having the strongest association. During antibiotic therapy and in the first month after, the risk for CDI was increased 7–10 times, but the risk declined at later times.
Secondary infection	(15)	Association between previous antibiotic exposure and blood stream infection by *C. galabrata* and fluconazole-resistant *Candida* isolates.	*C. galabrata* infection was strongly associated with metrodiazole exposure. Infection by fluconazole-resistant *Candida* isolates was associated with carbapenem, trimetoprim-sulfamethoxazole, clindamycin, and colistin exposure.
Secondary infection	(13)	Risk factors for ESBL-producing *Enterobacteriaceae* bloodstream infection, case-control study, Auckland, New Zeeland	Independent risk factors for ESBL-*Enterobacteriaceae* bacteraemia were fluoroquinolone exposure, first generation cephalosporins, and previously known ESBL-*Enterobacteriaceae* colonisation.

Secondary infection	(21)	The risk of necrotizing enterocolitis (NEC) in neonates after antibiotic exposure, retrospective case-control study, New Haven, USA	The risk of NEC was significantly increased with the duration of antibiotic exposure in children without prior sepsis. For septic neonates, antibiotics were protective against NEC.
Secondary infection	(16)	Association between antimicrobial use and campylobacteriosis, registry-based case-control study, Denmark	Campylobacteriosis risk was reduced 1 month after macrolide exposure and increased 1 month to 2 years before infection. Previous use of fluoroquinolones was also associated with increased risk for campylobacteriosis, and the risk was higher for resistant isolates compared to susceptible ones.
Secondary infection	(7)	The risk of trimethoprim and ciprofloxacin resistance after antibiotic treatment associated with *E. coli* urinary tract infection, prospective case-control study, Dublin, Ireland	The risk of resistant *E. coli* urinary tract infection increased with an increasing number of prescriptions over the previous year both for trimethoprim and, in particular, for ciprofloxacin.
Secondary infection	(20)	Risk factors for healthcare-associated pneumonia, review, New York and Texas, USA	Prior antibiotic use is one strong risk factor for drug-resistant organisms in healthcare-associated pneumonia patients.
Secondary infection	(1)	Collateral damage to the commensal flora mediated by antibiotic therapy, selection and spread of antimicrobial resistance and CDI, review, Switzerland and USA.	Antibiotics are associated with colonisation and infection with both gram-positive and gram-negative bacteria, often with resistance properties.
Secondary infection	(19)	Epidemiology of CDI infection in travellers, review, Israel	Prior use of antibiotics, especially fluoroquinolones, was a strong risk factor for CDI in travellers.
Inflammatory bowel disease/Irritable bowel	(24)	Association between broad-spectrum antibiotics and the development of IBS, retrospective cohort study, Rochester, USA	Use of broad-spectrum antibiotics, especially macrolides and tetracyclines, might be associated with IBS development.

syndrome (IBD/IBS)			
IBD/IBS	(22)	Association between childhood exposure to antibiotics and the development of IBD, case-control study, Finland	No association was seen between antibiotic exposure and ulcerative colitis. However, an association was found for Crohn's disease, especially after cephalosporin exposure.
IBD/IBS	(23)	Geographical variability and environmental risk factors in IBD, review, Hong Kong, Canada, Norway, Sweden, USA, Hungary, and Ireland.	At least nine studies have shown an association between prior antibiotic exposure and diagnosis of IBD, with a higher association for Crohn's disease than ulcerative colitis. Whether this is a causal relationship is still unknown.
Asthma, allergy, eczema, and rhinitis	(35)	Association between antibiotics during pregnancy and the risk for early childhood asthma, prospective cohort study, Copenhagen, Denmark	Increased risk for asthma exacerbation was shown for children to mothers exposed to antibiotics during the third trimester. Antibiotic exposure at any time of pregnancy showed increased risk of hospitalization and inhaled corticosteroids.
Asthma, allergy, eczema, and rhinitis	(29)	Genetic and environmental risk factors for early childhood allergic rhinitis, retrospective cohort study, Seoul, Korea	The use of antibiotics for more than 3 days during infancy was an independent risk factor for allergic rhinitis in school age children (first to sixth grade in elementary school).
Asthma, allergy, eczema, and rhinitis	(36)	Risk factors for early presentation of asthma among preschool children in Taiwan, retrospective cohort study, Taoyuan, Taiwan	Antibiotic use in young infancy and early infection of the respiratory tract were significant risk factors for asthma in pre-school children.
Asthma, allergy, eczema, and rhinitis	(25)	The association between broad-spectrum antibiotics in early childhood and wheezing and asthma in 5-year-old	Use of macrolides and cephalosporins in early childhood was significantly associated with asthma. However, overall use of antibiotics was not. Wheezing

		children, prospective cohort study, Krakow, Poland	episodes were only associated with macrolide exposure.
Asthma, allergy, eczema, and rhinitis	(32)	Association between antibiotic use within the first 6 months of life and asthma and allergy at 6 years, prospective cohort study, New England, USA	Antibiotic exposure was associated with increased risk of asthma, particularly in children with no family history of the disease.
Asthma, allergy, eczema, and rhinitis	(34)	Association between neonatal sepsis and antibiotic exposure and later risk of allergic disease, case-control study, Stockholm, Sweden	Asthma was more prevalent in children with earlier neonatal sepsis and early antibiotic exposure compared to a control group.
Asthma, allergy, eczema, and rhinitis	(26)	Association between antibiotic exposure before 1 year and the development of childhood asthma, longitudinal cohort study, British Columbia, Canada	Antibiotic exposure in the first year was associated with a small risk of early childhood asthma that increased with the number of antibiotic courses. All antibiotics showed this association with the exception of sulphonamides.
Asthma, allergy, eczema, and rhinitis	(31)	Prenatal or first year of life exposure to antibiotics and its association with childhood asthma, review, New Haven, USA	Antibiotics appear to slightly increase the risk of childhood asthma.
Asthma, allergy, eczema, and rhinitis	(27)	Association between pre- and postnatal exposure to antibiotics and eczema, wheezing, and atopic sensitizations in children, prospective cohort study, Belgium and Netherlands.	Exposure to antibiotics in utero and during lactation increases the risk of allergic symptoms in children, but direct exposure appears to be protective.
Asthma, allergy, eczema, and rhinitis	(33)	Association between early antibiotic exposure and infection and the risk of atopic eczema (AE), cohort study, Dresden, Germany	Infection per se does not seem to alter the risk of subsequent AE, however respiratory infections treated with macrolides and cephalosporins significantly increased the risk of AE.
Asthma, allergy,	(30)	Environmental and demographic risk factors for	Antibiotic use in infancy was not associated with egg allergy.

eczema, and rhinitis		egg allergy, population-based study, Australia	
Asthma, allergy, eczema, and rhinitis	(37)	Investigation of regional differences in the prevalence and risk factors of food allergies in European children, prospective cohort study, Germany, Lithuania, Italy, the Netherlands, UK, Poland, Iceland, Greece, Spain, and Ireland	There are differences in both prevalence of food allergies and antibiotic use in the nine countries participating in the study.
Asthma, allergy, eczema, and rhinitis	(28)	Association between perinatal factors and food allergies, retrospective chart review, Pennsylvania, USA	The study did not find perinatal antibiotics to be associated with increased risk for food allergies.
Obesity	(39)	Association between antibiotic exposure during the first 2 years of life and the development of body mass over the first 7 years, longitudinal cohort study, New York, USA	Exposure to antibiotics in the first 6 months is associated with increased body mass from 10 months to 38 months of age. However, on an individual level the effects are modest. Later exposure is not associated with increased body mass.
Obesity	(38)	The role of delivery mode, pre-pregnancy weight, and early administration of antibiotics on childhood overweight, longitudinal prospective study, Copenhagen, Denmark	Antibiotics during the first 6 months increased the risk of overweight in children born to normal-weight mothers and decreased the risk of children born to overweight and obese mothers.
Cancer	(41)	Association between antibiotic use and risk of cervical, ovarian, and uterine cancers, case-control study, Saskatchewan, Canada	Antibiotic exposure was significantly associated with reduced risk of cervical cancer. For ovarian and uterine cancers, no association with previous antibiotic exposure was found.
Cancer	(40)	Association between antibiotic exposure and the risk of prostate cancer, case-control study, Saskatchewan, Canada	Antibiotic exposure 1 year to 15 years in the past was associated with increased risk of prostate cancer, however no temporal trends or class-specific effects

			were found, and this suggests a non-causal relationship.

The objective with this report is to review and summarize recent studies concerning the adverse ecological effects of antibiotics on the commensal microflora of exposed individuals and the accompanying secondary diseases. The results are intended to be used by professionals in the health care sector in the context of antibiotic stewardship.

Det här är en systematisk genomgång av den vetenskapliga litteraturen om negativa ekologiska effekter av antibiotikaanvändning på individnivå. Den är tänkt som ett kunskapsunderlag att användas av lokala Stramagrupper, läkemedelskommittéer eller enskilda förskrivare i sammanhang när man diskuterar rationell antibiotikaanvändning. Rapporten är skriven på engelska för att också kunna användas i de internationella projekt om rationell antibiotikaanvändning som Folkhälsomyndigheten deltar i.

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