Establishing a link between antibiotics and asthma in early life

A discussion of the current work in BC linking antibiotic use in early infancy with the risk of childhood asthma, what the next steps are for this work, and what role clinicians from diverse specialties can play in combating the asthma and allergy epidemic.

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Current research in BC

Over the past 20 years, BC physicians have been responsible for an exemplary decline in antibiotic use in children under 5 years of age, most dramatically evident in infants under 1 year. Between 1996 and 2016, BC saw a 77% reduction in antibiotic prescriptions for infants.[1] This has been mainly due to reductions in antibiotic use in upper respiratory tract infections (URTI) and acute otitis media. Alongside improved stewardship efforts, we have also seen the parallel rollout of conjugate pneumococcal vaccine 7 (in 2010) followed by conjugate pneumococcal vaccine 13 (in 2015). A resulting reduction in bacterial upper respiratory tract infections may be further reducing the need for antibiotics.[2]

Antibiotic stewardship programs in hospitals and communities carry a primary aim of reducing inappropriate use to slow microbial selection toward more resistant strains and infections. However, there is now growing evidence that good antibiotic stewardship might also contribute to the prevention of some common chronic diseases as well, starting with asthma.

It is perhaps less well known that between 2000 and 2014 the incidence of asthma in children under 5 years declined by 26%, from 27.3 to 20.2 diagnoses per 1000 children.[3] This represents the first major reversal in the late 20th century trend of increasing incidence and prevalence. Collaborative work from the BCCDC, BC Children's Hospital, and UBC recently published in the *Lancet Respiratory Medicine*, demonstrated an association between antibiotic prescribing in infants under 1 year and incidence of asthma in children under 5 years at the provincial population level, with a projected 24% increase in asthma incidence for every 10% increase in antibiotic prescribing, after adjusting for year, sex, material and social deprivation indices, and ambient air quality indicators (PM2.5).[3] When this relationship was examined at the patient-level in a cohort of 2644 children through the CHILD study (a national prospective birth cohort), children who were

Key messages:

- Reducing early-life exposure to antibiotics may decrease the risk of childhood asthma by preserving the gut microflora responsible for training the immune system.
- Ongoing work in BC investigates this association in a retrospective provincial birth cohort using linked data to build a causal argument.
- Pediatricians, infectious disease specialists, pharmacists, allergists, and family physicians all have a role to play in promoting good antibiotic stewardship to potentially reduce the risk of childhood atopic disease.

exposed to antibiotics in infancy were 2.5 times more likely to develop asthma in childhood than children who weren't exposed. This remained true after adjusting for possible confounders such as ethnicity, mode of delivery, exposure to air pollution, sex, and parental atopic history. Interestingly, after excluding children who had received antibiotics for respiratory symptoms, to eliminate a concern that the relationship was confounded by the indication driving prescribing, this association remained and there was a significant dose-dependent response—namely, 5.2% of children not exposed to antibiotics in their first year of life developed asthma, compared with 8.1% of children who received one course, 10.2% of children who received two courses, and 17.6% of children who received three or more courses.

Making the link

How are antibiotics in infancy connected to childhood asthma? Increasing evidence points to the gut microflora, namely, perturbances to the initial seeding and colonization of the infant gut, otherwise known as microbial dysbiosis. Typically, the neonatal gut is seeded with commensal or beneficial bacterial species in a well-established series of ecological succession. These commensal bacterial species serve a number of functions in the first few months of life: their occupation of the gut helps prevent pathogenic bacteria from establishing a foothold, thereby helping to protect against infection, and their production of metabolites such as short-chain fatty acids (SCFAs) are considered to be a key driver of immunologic T cell activity alongside acting as a down-regulator of proinflammatory responses. In this way, a diverse commensal bacterial ecology in the neonatal gut not only protects against colonization with harmful bacteria but also helps to train a robust immune system and promote homeostasis, protecting against hyperallergic responses in the future.[4] The perturbance of this relationship is commonly referred to as the "microflora hypothesis."[5]

Neonatal gut seeding begins in utero through the placenta and cord blood, and continues with seeding during vaginal birth and through breastfeeding, skin contact, and interaction with the built and natural environment. Perturbances in these natural sources of microbial exposure can change the delicate ecology of the infant gut by altering microbial diversity at this crucial time of immune system development. Specifically, cesarean section, a lack of breastfeeding, and intrapartum and postpartum antibiotic use all effect this microbial exposure and have independently been associated with altered gut microbial ecology and subsequent allergic sensitization.[6-8]

Going forward for BC

Following publication of this BC study,[3] there is still much that we don't know. First, the provincewide element of the whole population study was ecological (the data were analyzed at the level of the local health authority), meaning individual differences related to the children, which might affect their likelihood of being prescribed antibiotics and/or developing asthma, could not be accounted for. Second, the patient-level element of the study was conducted within the CHILD Study birth cohort, and while patient-level factors could be accounted for, it involved a much smaller group (2644 infants) across Canada, raising questions about generalizability of the findings to BC. Additionally, allergic asthma is only one form of atopic disease; other markers of allergic sensitization were not investigated. This is important because allergic asthma is not the only atopic disease common in childhood; allergic rhinitis (hay fever), food allergies, and atopic dermatitis (eczema) are also immune-regulated allergic diseases mediated by IgE, which frequently present together alongside asthma (or in succession), otherwise known as "the atopic march."[9] Lastly, wider evaluations of the safety of large reductions in antibiotic use in BC infants need to be conducted to determine whether a floor exists, below which further reducing prescribing could cause harm.

For these reasons our Community Antimicrobial Stewardship team at the BCCDC and UBC School of Population and Public Health, with collaborators at BC Children's Hospital, have developed an in-depth research protocol to follow on from this work. The study outlines a patient-level, province-wide investigation designed to 1) validate the findings of the patient-level analysis in a much larger cohort, 2) expand the outcomes to include other markers of allergic sensitization, 3) perform a series of sensitivity analyses to interrogate the association between antibiotic use and atopic outcomes to work toward further building a causal argument, and 4) investigate whether there are patient safety concerns about infection related to reduced pediatric antibiotic use. This work will involve building a retrospective provincial birth cohort using anonymized data from all infants born in BC over a 10-year period (approximately 460 000), with follow-up from birth to age 7, along with data related to their parents. In BC we are able to take advantage of the data linkage capacity of Population Data BC, collecting relevant clinical, sociodemographic, and environmental information for each infant and their family across multiple linked datasets, namely Perinatal Services BC, MSP, DAD, PharmaNet, Vital Statistics (Births and Deaths), CANUE Air Quality, BCCDC Immunizations, and Citizenship and Immigration Canada. This will allow for our findings to be completely generalizable to BC children as our focus is the entire BC child population. We are also building collaborations to study this relationship in other provinces and countries to assure its generalizability.

One potential source of bias in studies investigating causation is confounding by indication. This occurs when it is not possible to determine whether it is the treatment (i.e., antibiotics) or the underlying condition being treated (i.e., URTI) that is putting the patient at risk of the outcome (i.e., asthma). In the *Lancet Respiratory Medicine* article, we addressed this by conducting an analysis where respiratory indications were removed. Our population-based cohort study will include several sensitivity analyses looking at atopic outcomes in children receiving antibiotics only for nonrespiratory tract infections, as well as in infants with respiratory tract infections who did and did not receive antibiotics. In this way we hope to tease apart the individual effects of infection versus treatment on atopy risk.

It takes a village

How can practising physicians continue to play a role? If antibiotic exposure is a modifiable risk factor for resistant infections and for asthma,

there are many ways to reduce the risk for our patients. These include:

- Widespread vaccine coverage (particularly the pneumococcal vaccine).
- Beta-lactam allergy de-labeling to interrogate allergy labels and encourage the use of viable first-line treatments.[10]
- Keeping up-to-date with antibiotic prescribing guidance (Bugs and Drugs www.bugsanddrugs.org).
- Emphasizing symptomatic treatment for self-limiting infections (most otitis media).
- Providing strong follow-up if initial management does not include antibiotics.

These practices not only contribute to preserving this precious resource and reducing the risk of antibiotic resistance, they are also cost effective. For example, after the introduction of the Do Bugs Need Drugs? program in BC, average monthly costs of antibiotics decreased by $18.9 per 1000 population, resulting in an annual savings for the province in 2014 of $83.6 million,[11] and this was taking only direct drug costs into account; savings to the wider health care economy were not considered. Once the association between antibiotic stewardship and the reduction of asthma risk has been more clearly articulated in the entire provincial pediatric population, the attributable cost savings will be amplified. We also need to communicate the importance of the connection between asthma and antibiotic prescribing to patients and the public. For example, a plain language social media graphic has been used in BC by the Antibiotic Wise program to explain the results of the study **[Figure]**.[3]

This ongoing work highlights the impact that successful antibiotic stewardship practices can have, not only on reducing the potential for antibiotic-related side effects, opportunistic *C. difficile* infection following antibiotic treatment, and selection of antibiotic-resistant bacteria, but also for reducing the risk of childhood asthma and possibly other immune-regulated conditions. The potential for mitigating long-term morbidity and increasing cost savings to global health care systems is enormous. To realize this potential, however, a concerted effort will be required across many clinical communities, including pediatrics, respiratory medicine, immunology, infectious disease, and general practice, to turn the tide on the asthma and allergy epidemic and begin to shift toward a future where asthma and other atopic diseases are substantially preventable, not just manageable. ■

Competing interests

None declared.

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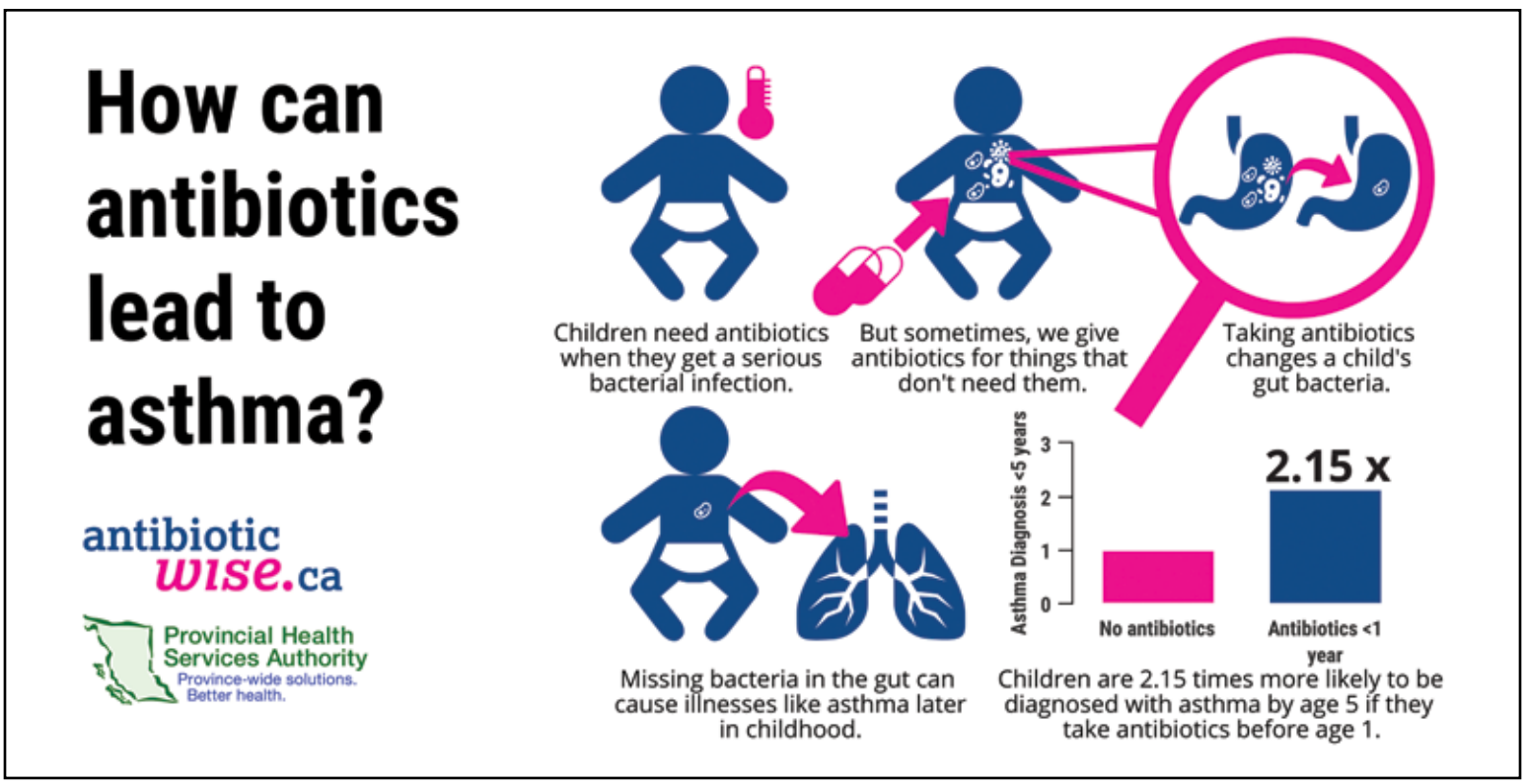

FIGURE. Graphic used in BC by the Antibiotic Wise program to explain the results of the Lancet Respiratory Medicine study.

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