"In medical school, we learned the names of bacteria and how to kill them with antibiotics," says Dr. Turvey.

"We are increasingly aware of the problem of antibiotic resistance and this new data highlights the risk of antibiotic overuse and asthma—we must be more careful about prescribing these important medications."

LOOKING AFTER LITTLE LUNGS

Avoiding antibiotics in infancy may protect against future asthma

At its Greek root, the word antibiotic means "against life" – as we use the word today, it means "against bacteria."

We used to think of bacteria as our enemies and early antibiotic researchers waged war against them. Beginning with the discovery of penicillin in 1928, antibiotics revolutionized the treatment of bacterial infections, enabling millions of people to survive illnesses such as pneumonia and tuberculosis, and significantly increasing life expectancy worldwide.

Dr. Stuart Turvey, Professor
The University of British Columbia

But there's a hefty downside to these lifesaving medications. Decades of overuse of antibiotics has allowed bacteria to build defense strategies and survive exposure to these drugs, meaning that some antibiotics no longer work against certain bacterial infections.

Experts have sounded the alarm about the danger of "antibiotic resistance," flagging it as one of the world's most pressing health threats and calling for antibiotics to be prescribed only when absolutely necessary.

In the Canadian province of British Columbia, physicians, health professionals and parents have heeded this call. From hospitals to health clinics and households, the use of antibiotics, especially in young babies, has significantly declined.

A new study by researchers from the BC Children's Hospital, the BC Centre for Disease Control (BCCDC), and The University of British Columbia (UBC) looked at the impact of this shift in practice and delivered some very good news: the declining use of antibiotics is doing more than slowing down antibiotic resistance – it may also be significantly reducing the incidence of childhood asthma.

Saying 'no' to unnecessary antibiotics in BC

Dr. Stuart Turvey, a pediatric immunologist and Aubrey J. Tingle Professor of Pediatric Immunology at UBC, was senior author of the study, published in June 2020, in *The Lancet Respiratory Medicine.* His co-authors included Dr. David Patrick, director of research and medical lead of the BCCDC's antimicrobial resistance program; and Dr. B. Brett Finlay, Peter Wall Distinguished Professor in the Michael Smith Laboratories and professor at UBC.

"In medical school, we learned the names of bacteria and how to kill them with antibiotics," says Dr. Turvey. "We now understand the problem of antibiotic resistance and we also know that antibiotic use is a risk factor for childhood asthma, so we have become much, much more careful in how we prescribe these medications."

Using population-level data from the 4.7 million people living in BC, Dr. Turvey and his colleagues found that between 2000 and 2014, there was a 40% reduction in antibiotic prescriptions to babies under one year of age – signifying a dramatic shift in the once near-universal practice of treating typical infant earaches, runny noses and sniffles with antibiotics.

During this same period, asthma rates decreased by about 26% among kids between one and four years of age. Looking at the data another way, the incidence of asthma rose by 24% with each 10% increase in antibiotic prescribing. "It's what we call a dose-response relationship, and it was striking in this case," comments Dr. Turvey. "It suggests that the reductions in antibiotic use and asthma were not coincidental. We were seeing something real."

"Asthma is a lung disease and bacteria live in our intestines, so it might seem strange to think that asthma and the gut microbiome are connected. However, gut bacteria play a really important role in training a baby's immune system," explains Dr. Turvey.

The researchers also looked at individual-level data from the more than 2,600 Canadian children with antibiotic use data participating in the CHILD Cohort Study (CHILD) – a national birth cohort study that is determining how an infant's genes, environment, and early-life exposures influence health and the development of chronic diseases such as asthma, allergies and obesity.

The results from the CHILD data were striking: babies treated with antibiotics in the first year of life had almost *double the risk* of being diagnosed with asthma by age five.

To ensure that they weren't dealing with "reverse causation"– meaning that the antibiotic use was triggered by asthma symptoms rather than *vice-versa* – the investigators undertook a sub-analysis that excluded children who received antibiotics for respiratory tract infections or who were diagnosed with infant wheeze (an early indicator of possible asthma). They saw the same result: babies who received at least one course of antibiotics during the first year of life were twice as likely to have asthma at age five.

Among kids who received antibiotics early in life, will the elevated risk of asthma persist as they get older? Dr. Turvey intends to find out. As co-Director of CHILD nationally, and as site leader for the study's regional site in Vancouver, BC, he has been working with the study's children and their families since 2008.

"One of the many strengths of CHILD is the parents' commitment to long-term participation in the study," he says. "We began CHILD when the mothers were pregnant, and a dozen years later the families are still excited to be contributing to this important research. The families are truly amazing, and we plan to continue following the kids along to see what happens with asthma and a host of other health outcomes as they get older."

Poster by CHILD participant Ella (8 years old), from Port Moody, BC

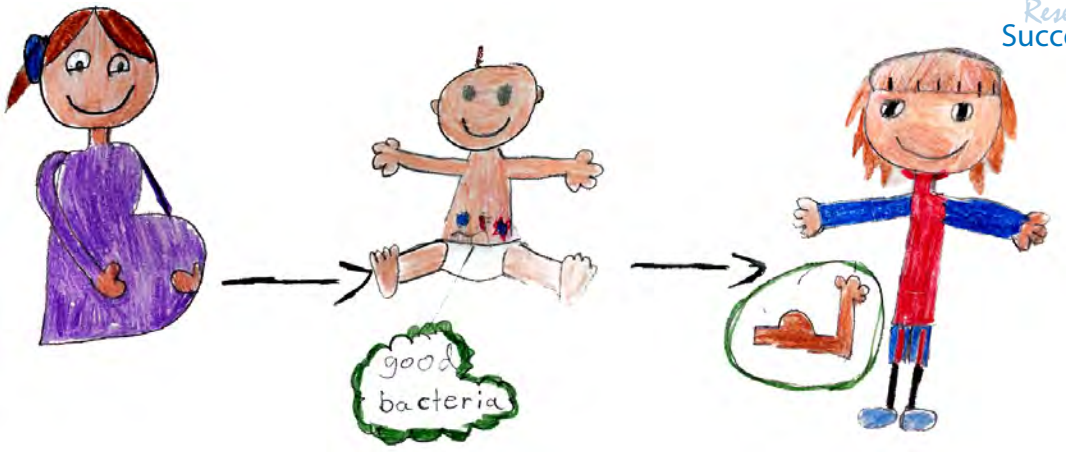
The gut "sits in the middle"

The Lancet Respiratory Medicine study set out not only to look at the association between antibiotics and asthma, but to uncover the *why* of this association. In a third level of analysis, the researchers examined the tiny microbes present in the children's guts (known as the gut microbiome) and observed the changes that occurred among them with antibiotic use.

"Asthma is a lung disease and bacteria live in our intestines, so it might seem strange to think that asthma and the gut microbiome are connected. However, gut bacteria play a really important role in training a baby's immune system," explains Dr. Turvey. "Previous research, including our own, has shown that imbalances in a baby's gut bacteria can increase the risk of asthma, so this seemed like a good area to investigate."

When CHILD participants were infants, research staff collected stool samples from their diapers. "It's this type of foresight that distinguishes CHILD from many other studies. From these samples, we can see what bacteria were living in the babies' guts at various time points. Imagine having access to this kind of valuable data? CHILD has huge freezers full of these amazing samples."

Using a DNA sequencing technique, the team was able identify categories of bacteria present in each infant's stool sample. As expected, the diversity of bacteria (in terms of both types and balance) increased significantly between three



Poster (detail) by CHILD participant Julian (9 years old), from Vancouver, BC

months and one year of age. "This happens with all babies as their diet becomes more complex," Dr. Turvey explains. But a telling difference emerged: kids who had asthma had lower bacterial diversity than kids without asthma.

What seemed to most influence this loss of diversity was the number and timing of a child's antibiotic exposures: diversity decreased with each additional course of antibiotics, and was low in babies who had their first dose of antibiotics before three months of age.

Taken together, these results supported Dr. Turvey's hunch that the gut "sits in the middle" of the antibiotic-asthma connection. The model looks like this: "When babies are born, bacteria that support their immune system begin to colonize their digestive systems. When some of these 'good' bacteria are wiped out by antibiotics, the immune system doesn't function properly, which can drive lung inflammation and lead to asthma."

"Avoiding antibiotics in the first year of life helps preserve the diversity and abundance of gut bacteria, making children less susceptible to developing asthma later in life," concludes Dr. Turvey. And what makes the first year so special? "It's when the gut microbiome is most malleable and subject to outside forces."

A better balance of bugs and drugs

Cradling a feverish baby who is pulling at his ears can upset even the calmest of parents. Antibiotics hold the promise of making it all go away. What parent hasn't been tempted to use antibiotics to treat their baby's ear infection? Or sore throat, or fever?

According to Choosing Antibiotics Wisely, a national campaign to help clinicians and patients engage in conversations about unnecessary antibiotic use, 30 to 50% of antibiotic prescriptions among Canadians remain unnecessary – even today, after antibiotic use has been on the decline.

Antibiotic stewardship – a push for the careful and limited use of antibiotics to slow the development of drug-resistant organisms – is seeking to further stem this excess. Dr. Turvey's study bolsters the case: curtailing antibiotic use not only preserves the effectiveness of these medications, but it may prevent asthma in at least some children. In fact, "public messaging about antibiotic stewardship is moving beyond the 'superbug resistance story'," he affirms. "Advisory groups are starting to talk about lowered asthma rates and other 'unanticipated benefits' of limiting antibiotic use."

The study could also change the management of infants who really need to take antibiotics. For example, in the future, perhaps doctors could give these infants carefully designed probiotics, or specific "good" bacteria, to replace those wiped out by the medication.

A similar approach could help in the fight against asthma. "Once we identify a child at high risk for asthma, we could replenish the specific missing bacteria in its gut and theoretically reduce the risk," he says.

Meanwhile, CHILD's impressive output of scientific findings has garnered the study additional support, including a grant of over $9 million from Genome Canada, the Canadian Institutes of Health Research (CIHR), and other partners. This funding is allowing Drs Turvey and Finlay, and their teams, to further study the "missing" gut microbes associated with asthma and to develop a screening tool to identify infants at the highest risk of asthma.

"We're very excited about taking this next step toward our goals of identifying babies at risk for asthma and devising new treatments that would prevent the development of this chronic disease," says Dr. Turvey.

"While antibiotics are 'against life,' lungs are for life – and we want to do our best to look after them, especially in kids!"