Winter 2021

CHILD COHORT STUDY

Helping kids grow up healthy

SCREEN TIME
How much is too much?

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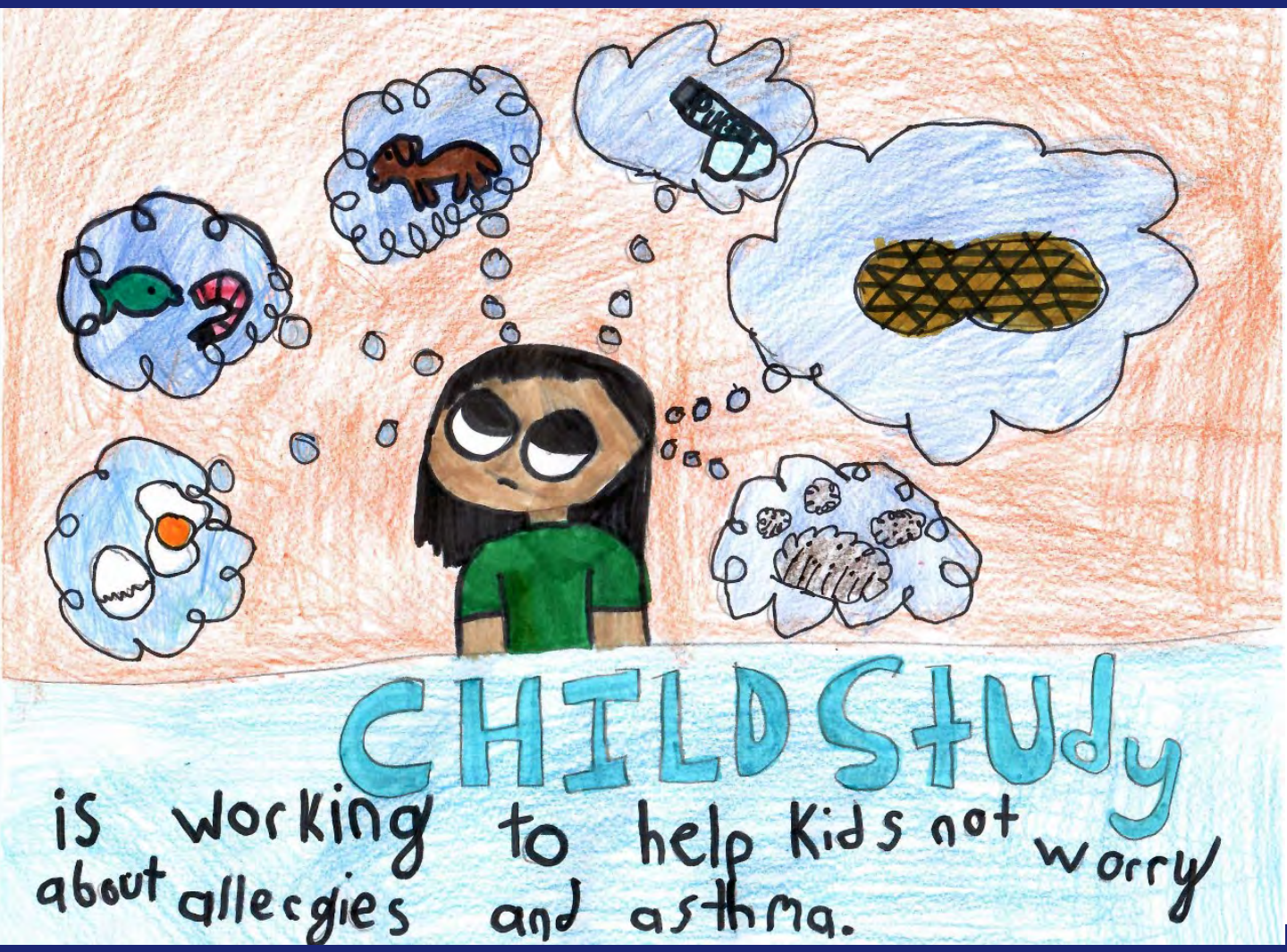

Poster by CHILD Cohort Study participant Andy (8 years old), from Toronto, ON

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Helping kids grow up healthy

The CHILD Cohort Study, or CHILD, is a world leader in maternal, newborn and child health research.

Launched in 2008 with foundational funding from the Allergy, Genes and Environment (AllerGen) Network and the Canadian Institutes of Health Research (CIHR), and ongoing funding and support from AllerGen, CHILD follows the lives of nearly 3,500 children (and their parents) over time as they grow and develop – from mid-pregnancy into childhood, adolescence and beyond.

CHILD is a general population longitudinal birth cohort study, meaning that the researchers make detailed observations about the health, development and well-being of study participants in real time. Every few years, CHILD research teams conduct extensive physical, cognitive and psychosocial assessments with the participating children. So far, CHILD has collected over 40 million data points from more than 500,000 questionnaire responses and 600,000 biological samples.

By analyzing the data, researchers have been able to identify genetic and environmental factors in early life that affect the development of allergies, asthma, obesity, diabetes, the immune system and internal microbiome, as well as neurodevelopment and mental health.

CHILD has four study sites located in: Vancouver, British Columbia; Edmonton, Alberta; Winnipeg and Morden/ Winkler, Manitoba; and Toronto, Ontario. The Study headquarters are located at McMaster University in Hamilton, Ontario.

Now in its 12th year, CHILD has produced over 100 scientific publications with breakthrough findings that have been featured by global media outlets including *TIME Magazine*, *People*, *Vogue*, *New York Times*, *Wall Street Journal, CBC*, *Globe & Mail*, and *Maclean's*.

CHILD's *Research Success Stories* shares these stories with Canadian families, health professionals, policymakers and community organizations. Each issue highlights new CHILD research results that have the potential to impact personalized medical practice, parenting choices, consumer product regulations and policy development for healthy communities.

We hope you find these stories interesting and informative.

About AllerGen NCE

The Allergy, Genes and Environment (AllerGen) Network was established in 2004 to unite Canada's allergic and respiratory disease communities with the overall goal of improving the lives of Canadians living with asthma, allergies, anaphylaxis and related immune diseases.

Throughout AllerGen's 15 successful years (2004-2019) as a national Networks of Centres of Excellence, the Network's research teams generated new knowledge, advanced drug development, laid the groundwork for significant future discoveries, and expanded research and clinical training opportunities for a new generation of leaders in the field.

The CHILD Cohort Study is an AllerGen Legacy Initiative that has become a critically important discovery platform answering questions about the origins of chronic diseases and identifying early life "critical windows" to build healthier futures.

About CIHR

Created in 2000 under the authority of the CIHR Act, the Canadian Institutes of Health Research (CIHR) is the Government of Canada's health research investment agency that seeks to respond to the evolving needs for health research.

Diana Royce, EdD
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CHILD Cohort Study Co-Director

"Children who spent more of their day in front of screens were *seven times* more likely to meet the criteria for ADHD ," says Dr. Mandhane.

SCREENS AND CONSEQUENCES

Researchers at CHILD's Edmonton site have taken a close-up look at screen time in preschoolers and found that quantity matters – a lot

How many screens did you grow up with? Almost certainly, a television and calculator; possibly a personal computer and digital watch. Depending on your age, the Internet didn't exist or was just ramping up.

Now, think of children growing up today: in all likelihood, there are several laptops and tablets in their homes, online games teach them the alphabet and counting, and an older sibling's smartphone winks at them from the kitchen counter. Even toddlers are awash in screen-based content from interactive apps to music and stories.

Dr. Piush Mandhane, Associate Professor
University of Alberta

Dr. Sukhpreet Tamana, Research Associate,
Simon Fraser University

Restrictions on everyday activities during the coronavirus pandemic have meant that many parents have turned to television, tablets and video games to entertain their kids more than they typically would. Parents, healthcare providers and educators may be left wondering: How much screen time is too much?

Dr. Piush Mandhane, an associate professor of pediatrics at the University of Alberta, was intrigued by this question, even before the pandemic. In 2019, he studied the effects of screen time in 2,400 young children across Canada using data from the CHILD Cohort Study (CHILD).

Launched in 2008, CHILD is an ongoing national birth cohort study that is tracking the health and development of nearly 3,500 children from before birth to the teen years and beyond. With more than 600,000 questionnaire responses and 500,000 biological samples already collected from participating families, CHILD is one of the most informative studies of its kind in the world. Dr. Mandhane leads the Edmonton site of CHILD.

Dr. Mandhane's screen time research found that, compared to children who spent less than 30 minutes per day with screens, young children who had more than two hours of screen time per day were over *seven times more likely* to meet the criteria for attention deficit hyperactivity disorder (ADHD). They were also five times more likely to exhibit unwanted behaviours such as inattention and aggression.

It was the largest study in Canada to look at the impact of screen time exposure among preschoolers – and it all started with sleep.

An awakening hypothesis

In an earlier study, Dr. Mandhane and his team discovered that infants who slept less than 12 hours over any given 24-hour period had poorer cognitive and language development at two years of age compared to infants who got more sleep. The timing of the sleep mattered too: nighttime sleep had the greatest impact. "A short nighttime sleep was associated with a 10-point drop in a child's cognitive skills," says Dr. Mandhane. "That's nearly a full standard deviation, which is quite a substantial difference."

The discovery about sleep led to a theory about screen time. Dr. Sukhpreet Tamana, a post-doctoral student working with Dr. Mandhane, noticed that data collected by CHILD included information about screen time.

"There wasn't a lot of research out there looking at screen time in preschoolers, and we wondered if screen exposure might have something to do with our sleep findings," says Dr. Tamana, who now works as a research associate at Simon Fraser University.

Looking through the data, they observed that television time and poor sleep overlapped. "Kids who watched a lot of TV went to bed later and had less sleep," she explains. "This led us to our next question: How much screen time is too much?"

Along with behaviours typical of ADHD, anxiety and withdrawal also showed up more often in children with screen use of two or more hours per day. Each additional increment of screen time between 30 and 120 minutes added to the risk of these behaviours.

To answer the question, the researchers went back to CHILD's vast database. Parents involved in the Study had provided detailed information about their children's screen time use – including TV, DVDs, computers, video consoles, smartphones and tablets – as well as how much time their children spent engaged in organized physical activity and how many hours their children typically slept at night.

"Five more minutes, Mom!"

The researchers found that, on average, three-year-old children spent 1.5 hours a day in front of a screen, while five-year-olds spent an average of 1.4 hours a day. For both ages, the average daily screen time use exceeded Canada's 24-Hour Movement Guidelines.

"Among the younger kids, 42% of three-year-olds exceeded the recommendation of less than one hour of screen time per day. For five-year-olds, 13% of the children exceeded the recommendation of less than two hours of screen time per day," reports Dr. Tamana.

Parents participating in CHILD also completed a 99-item checklist about their child's behaviour at age five, covering everything from aggressive behaviour to social withdrawal to sleep. Dr. Mandhane's team was most interested in "externalizing behaviours" – an umbrella term used to describe behaviours that reflect a lack of inhibitory control, including inattention, hyperactivity, and aggression. They also looked for clusters of responses that pointed to clinical diagnoses such as ADHD or oppositional-defiant disorder.

Using a statistical test, the team looked for connections between screen time and behaviour at age five, and considered variables such as physical activity, sleep duration, and sleep-disordered breathing in the analysis.

What does the research say?

Although Dr. Mandhane had expected to find some connection between screen time and behaviour, the magnitude of the effect came as a surprise. "Children who spent more of their day in front of screens were seven times more likely to meet the criteria for ADHD," he says.

Along with behaviours typical of ADHD, anxiety and withdrawal also showed up more often in children with screen

use of two or more hours per day. Each additional increment of screen time between 30 and 120 minutes added to the risk of these behaviours.

The researchers also looked for protective factors that made behavioural problems less likely. They found that more than two hours a week of physical activity significantly reduced children's risk of behavioural problems at age five. Not just any physical activity, though. "It had to be structured physical activity, such as organized sports," says Dr. Mandhane. "Just running around or shooting hoops didn't protect children in the same way." Why structured? "We don't know for sure yet, but it's possible that the structure and routine of organized activity may help promote positive behavioural development."

A good night's sleep also offered some protection, confirming the link that Dr. Mandhane's previous research had uncovered. Specifically, children who met the recommendation of 10 hours of more of nightly sleep had a reduced risk of behavioural problems at age five, though the benefit was small compared to low screen time.

"This means we can't explain the impact of screens entirely through sleep disruption," he concludes. What could it all mean, then? "It's possible that interacting with screens affects how the brain wires itself in childhood," says Dr. Mandhane, conceding that this is speculation until further research can fill in the blanks.

For now, "we have simply shown a correlation between screen time and behavioural problems, and we cannot say forsure that one causes the other."

Joining the "tech" conversation

The research was published by the scientific journal *PLOS ONE* in April 2019 and made a splash in the mainstream media. From *CBC News* and *The Globe and Mail* to *People.com* and *Newsweek*, major news outlets picked up the story and invited Drs Mandhane and Tamana to comment on their findings.

The study's ripples have also extended beyond the media. A US tech company working on a new app to help children with reading and other learning tasks approached Dr. Tamana "wanting input on whether they should limit children's use of the app." Dr. Tamana invited them to consider building time limits into the software, rather than allowing children to blast through the levels without any constraints. "I found it exciting that developers were starting to think about this – that our work was becoming part of the conversation," she says.

According to Dr. Mandhane, research like this would not be possible without CHILD's incredible database of information on children's early life exposures and later health outcomes. CHILD has collected more than 40 million datapoints and its questionnaire responses span dozens of topics, including birth factors, nutrition, sleep, environmental exposures, bullying, school performance, body image and gender self-identification, among many others.

No guilt, just limits

Dr. Mandhane sees the screen time study as a springboard to new investigations. Questions he plans to address in future studies include: Does the timing of screen use matter? Do viewing binges have different outcomes from steady use? Does it make a difference whether the child uses screens to play games, learn about ancient history, or chat with friends? Dr. Mandhane also hopes to follow the CHILD cohort of children as they grow up, to see if the association between screen time and behaviour persists over the years.

In the meantime, he recommends that screen time be limited to less than two hours a day for young children and he regards the preschool years as "the ideal time to promote healthy relationships with screens."

In practical terms, this could mean putting timers on devices, setting rules about using screens at specific times or days, or putting screens away well before bedtime. He also encourages adults to help children balance screen time with organized physical activity.

And what to do during the pandemic, when restrictions on activities have brought many children closer to screens than ever? "Parents should not feel guilty during this time," Dr. Tamana offers. Instead, "We suggest that they set up a routine that breaks up the screen time with activities such as indoor and outdoor play, arts and crafts, games, or quiet-time activities such as reading or story time."

Even outside the context of a pandemic, the researchers recognize that screens have a significant place in modern life, especially as children get older and use screens to connect with their peers. "Screens are to today's teens what telephones were to my generation," Dr. Mandhane points out. "We can't just forbid them from using all screens." As with so many things in life, "it's a question of balance."

"We expected to see a difference in asthma risk between breastmilk-fed and formula-fed infants," says Dr. Azad. "However, we were surprised to find that for the breastmilk-fed babies, *how* the babies received breastmilk seemed to matter."

BREASTMILK:
Best Served Straight from the Source

Researchers from CHILD's Manitoba site have discovered a new benefit of breastfeeding.

Reduce infections and illnesses? Yup. Lower the risk for sudden infant death syndrome? Check. Protect against childhood asthma and obesity? Yes, that too.

As most of the world knows by now, breastmilk has been called the "perfect food" for babies. Dr. Meghan Azad, an associate professor and Canada Research Chair in the Developmental Origins of Chronic Disease at the University of Manitoba, has been studying this "perfect food" for years.

Dr. Meghan Azad, Associate Professor
University of Manitoba

Dr. Shirin Moossavi, Postdoctoral Fellow
University of Calgary

"Each mother produces breastmilk uniquely tailored for her baby – I think that's kind of like a superpower," says Dr. Azad. Moms get many benefits from breastfeeding their infants too, including reductions in anxiety, negative mood, and stress. "Breastfeeding is one of those special experiences that can improve mental health and behaviour in not just one, but in two people at the same time," she notes.

Until recently, however, scientists had little reason to think that the way breastmilk reaches the baby is important. Whether it's delivered from the breast or a bottle, it's been assumed that breastmilk provides the same benefits.

However, in a series of research discoveries, Dr. Azad has changed this assumption. As an investigator with the CHILD Cohort Study, she has shown that nursing directly at the breast may be more beneficial than drinking pumped breastmilk from a bottle.

To suckle or to pump … that is the question

The first discovery came in 2017. Dr. Azad and her colleague Dr. Annika Klopp, a pediatrician at the University of Manitoba, analyzed data from more than 3,200 moms and babies and found that babies fed only at the breast for the first three months of life had a lower asthma risk than babies fed expressed breastmilk from a bottle.

"We expected to see a difference in asthma risk between breastmilk-fed and formula-fed infants, which we did," says Dr. Azad. "However, we were surprised to find that for the breastmilk-fed babies, how the babies received breastmilk seemed to matter."

While more research is needed to explain their results, the researchers have a couple of theories. "One possibility is that babies may develop stronger lungs through the physical act of suckling at the breast, which requires more effort than feeding from a bottle," says Dr. Azad. "Another theory is that the steps involved in pumping and storing breastmilk might negatively affect the milk's special cells, proteins and molecules that help to protect against asthma."

Another finding followed a year later. In a separate study, Dr. Azad's team found that babies nursed directly at the breast had a lower risk of obesity within their first year of life compared to babies who received breastmilk from a bottle. That decreased risk may eventually translate into a lowered chance of becoming overweight or obese later in life, according to the researchers.

The findings were published in the journal *Pediatrics* and picked up by international media outlets including *People*, *CNN*, *Global News*, *CBS News*, the *Boston Globe*, and the *Chicago Tribune*.

Dr. Azad is quick to note that expressed breastmilk still proved more beneficial than infant formula in both the asthma and obesity studies. "Moms go through a lot of effort to pump

breastmilk for their babies, and I wouldn't want them to get the impression that it's not worth it – there are definitely health benefits to pumped breastmilk over formula feeding."

Still, she was intrigued by the differences they saw and set out to better understand the factors influencing the benefits of breastmilk. "It would be great to be able to share with moms the best way to pump, store and feed breastmilk so as to maximize the benefits for babies who are not directly breastfed."

Learning from CHILD

The breastmilk samples and data Dr. Azad uses in her research come from the CHILD Cohort Study (CHILD) – a longitudinal birth cohort study that has been following nearly 3,500 Canadian children as they grow and develop from mid-pregnancy into childhood, the teen years … and possibly beyond. Dr. Azad co-leads the CHILD site in Manitoba – one of four provinces involved in the Study.

By collecting biological samples and information at critical timepoints in childhood, CHILD has enabled the identification of early-life factors that influence a child's health and well-being later in life.

When CHILD participants were infants, research staff collected breastmilk samples from the mothers as well as stool samples from the babies' diapers. In Dr. Azad's experience, "it's rare for a study to have the forethought to collect these unique biological samples – that's what makes CHILD so valuable as a research discovery platform." By analyzing the babies' stool, Dr. Azad and other CHILD researchers have been able to pinpoint the different communities of microbes found in each infant's gut.

To build on her previous discoveries, Dr. Azad went back to CHILD's vast repository of biological samples. She began by looking closely at breastmilk itself.

"Pumped breastmilk gives baby many of the same health benefits as nursing – it's just that nursing may have a slight edge," says Dr. Azad.

Not so sterile

Dr. Azad knew from previous research that breastfeeding gives a boost to a baby's developing gut microbiome – the collection of bacteria in a baby's digestive system. She just didn't know how that happened.

Until about 10 years ago, scientists believed that breastmilk was sterile, but ongoing research has altered this thinking: breastmilk actually contains live bacteria, including the "good" kind that support a baby's growing immune system and healthy metabolism.

Dr. Azad wondered if there was a link between a mom's milk bacteria and the bacteria in her baby's gut. "Our initial question was, what does the milk bacteria profile really look like?" she says.

To help her find out, Dr. Azad recruited Dr. Shirin Moossavi, then a PhD student working in a microbiome lab that studied dairy milk. An MD with an abiding interest in the microbiome, and now a 2020 Canadian Institutes for Health Research (CIHR) Postdoctoral Fellow at the University of Calgary, Dr. Moossavi harnessed the capacity of the lab to analyze the microbes in nearly 400 human breastmilk samples from CHILD. "We saw that it was highly variable – milk from different mothers contained different types and combinations of bacteria," says Dr. Moossavi. "So, our next question was, why the differences?"

Using information collected from the mothers, Drs Azad and Moossavi analyzed factors that might influence the milk bacteria. They considered whether the mother delivered vaginally or by C-section; her weight, age, diet, and ethnicity; and breastfeeding practices, such as exclusivity, duration and the method of feeding.

They were intrigued to discover that milk bacteria were different in mothers who pumped their milk compared to those who fed their infant directly from the breast. In fact, of all the variables they analyzed, breastmilk pumping was the one factor consistently associated with differences in milk bacteria. "This may offer us a clue as to why babies who consume pumped breast milk are at greater risk of asthma, allergies and early obesity than those who feed straight from the breast," says Dr. Moossavi.

How to explain the results? Drs Azad and Moossavi suspect that pumping may prevent the transfer of bacteria from the infant's mouth to the mother – in other words, when a baby is nursed, the baby's saliva can creep back into mom's nipple, and "this transfer may be prevented if the baby is fed from a bottle," explains Dr. Moossavi. Pumping might also introduce other bacteria from the pump itself, which could alter the bacterial profile in mom's milk.

The research was published in the journal *Cell Host & Microbe* and was one of its most cited papers in 2019. As the paper's first author and architect of the statistical methods used in the study, Dr. Moossavi "found it gratifying to hear back from people who applauded our methodology and rigour."

The paper also drew a lot of interest from mainstream media, including from *CBC*'s *Quirks and Quarks*. As often happens in translating research for the public, however; "some reports exaggerated the implications of the study and cast pumping in a somewhat negative light," says Dr. Azad. "But that's not what people should conclude from our research. Pumped breastmilk gives baby many of the same health benefits as nursing – it's just that nursing may have a slight edge – and we want to understand why, in order to provide helpful advice to moms who pump."

Gut reactions

Their findings prompted several more intriguing questions, including: Is mom's breastmilk bacteria shared with her baby? If so, how does it get there?

There was one way to find out: by comparing the bacteria in mom's breastmilk to the bacteria in her infant's gut. CHILD researchers had already profiled each baby's gut bacteria from stool collected in the diaper, "so it was just a question of looking at the bacteria in the breastmilk and connecting the dots," says Dr. Azad.

To do this, Drs Azad and Moossavi teamed up with CHILD colleagues from The University of British Columbia (UBC). The collaborative study was co-led by Dr. Stuart Turvey, Co-Director of CHILD and a pediatric immunologist and investigator at BC Children's Hospital; and Dr. B. Brett Finlay, Peter Wall Distinguished Professor in the Michael Smith Laboratories Laboratories and professor at UBC. Research trainees Kelsey Fehr at the University of Manitoba, and Drs Rozlyn Boutin and Hind Sbihi at UBC, along with Dr. Moossavi, were co-first authors of the publication, also published by *Cell Host & Microbe* in August 2020.

The team's working hypothesis proved correct: a mother's breastmilk and her infant's gut microbiome shared some of the same bacteria, including bacteria that previous CHILD research by Drs Finlay and Turvey found to protect against asthmatic wheeze.

"It's not just nutrients and immune components that moms transfer to their babies through breastmilk; they also seem to transfer 'good bacteria' that protect babies from illness and infections," comments Dr. Azad. "Our study also showed that the co-occurrence of shared 'good' bacteria was higher when infants nursed directly at the breast."

Dr. Azad believes that this latest research supports their earlier hypothesis that the process of pumping, storing and bottle-feeding breastmilk may reduce the transfer of viable milk bacteria from mom to baby. The results also support the idea that breastmilk may act as an incubator that protects and transports certain bacteria to a baby's intestinal tract. "This also gives us some idea as to which bacteria could make good probiotics, since they appear to withstand the trip to the baby's gut," she adds.

Questions Dr. Azad hopes to answer in future studies include: How might breastfeeding affect a baby's behaviour and brain development? Can a mother's diet while breastfeeding help prevent childhood allergies? How can we improve recommendations on handling and storing human milk for 'real-world' scenarios where many moms need to or choose to pump?

Even more importantly, how can the health benefits of breastmilk be provided to all babies – even those who are not fed breastmilk at all?

A $6.5 million grant awarded to Dr. Azad by the Bill & Melinda Gates Foundation will help advance these investigations. As Director of the newly created International Milk Composition (IMiC) Consortium, Dr. Azad will use the grant to study maternal nutrition and infant health in Canada and four other nations at various stages of development.

In the meantime, "I would like to see policies that support greater choice in feeding practices," says Dr. Azad. For example, "New mothers returning to work may feel that they have no choice but to pump, but we could be looking at ways to enable them to nurse."

Among her many current projects, Dr. Azad is looking at how to best teach children about breastfeeding, "so they grow up understanding that this is simply the normal way to feed babies," she adds. "It's never about coercing behaviour, but about helping people make informed choices and providing access to support – that's something we can all be part of.

“In our study, none of the infants introduced to peanut before six months of age were sensitized to peanut at age three, ” says Dr. Simons.

PASS THE PEANUT, PLEASE!

How to protect a baby from developing peanut allergy? Start with some peanut-based foods.

Introducing peanut to infants might sound like a scary thing to do. Especially since initially, parents were instructed to hold off serving peanut until after a baby's first year.

Today, parents are being told the opposite: Get babies eating peanut ASAP. What happened? Why such a dramatic shift in thinking?

In a nutshell: more research. After years of study, scientists now have a clearer understanding about the best time to introduce potentially allergenic foods like peanut to infants – and earlier is better. A lot better.

Dr. Elinor Simons, Assistant Professor
University of Manitoba

In 2019, a research project led by Dr. Elinor Simons, a clinician-scientist at the Children's Hospital Research Institute of Manitoba (CHRIM) and assistant professor at the University of Manitoba, is one of several large studies to reach this conclusion.

Dr. Simons' research found that babies who did not consume an age-appropriate form of peanut before their first birthday were four times more likely to be allergic to peanut by age three, compared to those little ones who ate peanut in their first 12 months.

"What makes our study unique is that we looked at children from the general population, not just kids believed to be at high risk of developing food allergy – as had been done in other studies," says Dr. Simons. "This means we now have evidence that early exposure to peanuts protects *all* children, not just those considered most at risk."

A serious problem of unknown origin

This can only be good news, because peanuts are hard to avoid. They're handy, inexpensive, tasty and a solid source of protein. But they sure can cause trouble if you're allergic to them.

In April 2020, a nationwide survey published by investigators from the Allergy, Genes and Environment (AllerGen) Networks of Centres of Excellence found that 3.2% of Canadian children have what is considered to be a "probable" peanut allergy.

Yet, the causes of peanut allergy are still largely unknown. A prevailing theory, known as the microbial hypothesis, suggests that a variety of environmental factors can disrupt a child's microbiome (the trillions of microbes that live on and in our bodies), causing the immune system to overreact to a food or a substance in a food.

Another theory suggests that exposure to allergens through the skin can increase the chance that an allergy will develop down the line. "This can happen in children with eczema; their skin may have a more fragile barrier and crack in places where food allergens, like peanut, can get into the body and make contact with the immune system through a route that does not usually allow development of tolerance," Dr. Simons explains. "For most infants, multiple factors likely contribute to development of sensitivity or tolerance to food allergens."

Despite the uncertainty about why peanut allergy develops for any given child, virtually everyone agrees on the seriousness of the problem. Health Canada lists peanut among its priority food allergens – the foods that cause the majority of allergic reactions – and federal labelling laws require peanut to be listed in the ingredient information on packaged food.

Poster by CHILD participant Oliver (8 years old), from Vancouver, BC

LEAPing to new conclusions

In recent years, several high-profile studies have determined that early exposure to peanut is beneficial to babies who are at high risk of developing peanut allergy – a group that includes infants with other food allergies or eczema.

One of the best known of these studies, the UK's Learning Early About Peanut (LEAP) study, found that feeding peanut to young infants with a heightened allergy risk reduced the likelihood, by 70 to 80%, that these children would develop a peanut allergy by age five.

"The LEAP results were very encouraging," notes Dr. Simons. "As a pediatric allergist, there are few interventions I can recommend to high-risk patients that will reduce the risk of a chronic allergic disease by a magnitude of 80%."

What science was still wondering, and what Dr. Simons was eager to find out, was whether early peanut introduction could also benefit children with a low risk of allergy. The Enquiring About Tolerance (EAT) study from the UK had suggested lower allergy development among breastfed infants randomized to early introduction of highly allergenic foods, inspiring Dr. Simons to investigate this area further.

Dr. Simons is a clinician investigator with the CHILD Cohort Study (CHILD), a unique Canadian research project that has been studying the health and development of close to 3,500 children across the country. By following these children from before birth, CHILD researchers have made exciting discoveries about how early-life exposures affect the development of childhood allergies, asthma, obesity and other chronic diseases.

As part of the ongoing data collected by CHILD, parents and caregivers provided detailed information about their children's consumption of potentially allergenic foods, including peanut, while also reporting on signs of food allergies the children developed along the way. At ages one, three and five, the children had skin prick testing to check for allergic sensitization (a marker for possible allergy) to peanut, egg, and cow's milk.

This gave Dr. Simons and her team the data they needed for their analysis. Unlike the LEAP study, CHILD participants were generally not at high risk for peanut allergy. When the small number of children who would have been part of the high-risk group studied by LEAP were excluded from the

analysis, the results did not change. In total, Dr. Simons' study involved 2,600 CHILD participants.

"Our results clearly showed that eating peanut early, even for low-risk children, reduced the incidence of peanut allergy later on," she explains. "In our study, none of the infants introduced to peanut before six months of age were sensitized to peanut at age three."

In fact, the benefit of introducing peanut early persisted as the babies grew. The babies who had not been introduced to peanut before 12 months of age were *four times* as likely to be allergic to it by age three. Children who did not have peanut introduced into their diet by 18 months were over *seven times* more likely to be sensitized or to exhibit an allergy to peanut compared to children who began consuming it before nine months of age.

"This finding tells us that if peanut has not been introduced before the age of 12 months, it should still be introduced as soon as possible," Dr. Simons adds.

The analysis also accounted for other factors that might contribute to the development of peanut allergy, such as family history and the number of older siblings. The *Journal of Allergy and Clinical Immunology: In Practice* published the study in November 2019.

The study's findings are in line with previous CHILD research, which found, in June 2017, that delaying the introduction of potentially allergenic foods increased the likelihood of a child developing a positive skin prick test to highly allergenic foods by age one.

In the 2017 study, infants who avoided cow's milk products, egg or peanut in their first year were nearly twice as likely to be sensitized to those foods compared to infants who consumed them before 12 months of age. Of interest, early introduction of egg before one year seemed to be especially beneficial – reducing allergic sensitization to all three foods, milk, egg and peanut – at 12 months.

The early bird ... doesn't get the allergy

Results from LEAP and other studies prompted the American Academy of Pediatrics (AAP) and the National Institute of Allergy and Infectious Diseases (NIAID) to update recommendations on introducing peanut. The new approach recommends introducing peanut-containing foods to babies at high risk for food allergy when these babies are between four to six months old, and to continue exposing them to peanut regularly through age one. The guidelines caution, however, that peanuts and peanut butter are choking hazards, and that smoothing peanut butter into pureed fruits or vegetables is a safe way to offer peanut to babies.

"Some parents are still worried about giving their infants potentially allergenic foods. If our study helps parents overcome this fear, it will have done its work," says Dr. Simons.

In 2019, the Canadian Paediatric Society (CPS) updated its guidance on peanut introduction as well. The new recommendations encourage the introduction of non-choking forms of peanut to high-risk infants when they are around six months old, but not before they reach four months of age.

And for infants with no particular risk for peanut allergy? Parents and caregivers should feel reassured about offering peanut early to them too, Dr. Simons advises. "Some parents are still worried about giving their infants potentially allergenic foods. If our study helps parents overcome this fear, it will have done its work," she says.

As she continues to follow the CHILD cohort children as they grow and develop, Dr. Simons expects more answers to the puzzle of peanut allergy to fall into place. "We're planning to follow these children to see if the benefit of early peanut introduction persists as they get older," she says.

In the meantime, in the fight against peanut allergy, "early introduction of peanut is an easy and natural tool that parents can use for all children."

Poster (detail) by CHILD participant Benjamin (8 years old), from Winnipeg, MB

"We found that babies more frequently exposed to cleaning products in their first few months of life had a higher risk for asthma and other breathing problems by age three," says Dr. Takaro.

CLEAN HOUSE, CONSTRICTED AIRWAYS

Not all cleaning products are created equal – and new research shows that frequent use could predispose children to developing asthma

Walk through the cleaning aisle in a supermarket and you'll find a product for every cleaning need: a lemony spritz to wipe down kitchen counters, a dazzling blue liquid for getting windows to shine, a scouring foam to clean ovens, a lavender-scented spray to freshen the air ... and the list goes on.

But some cleaners can do more harm than good. For instance, exposure to certain chemicals in household cleaning products has been linked to the development of asthma in adults. One might wonder, then: How safe is it to use cleaning products around kids?

Dr. Tim Takaro, Professor
Simon Fraser University

Jaclyn Parks, Graduate Student
Simon Fraser University

Research led by Dr. Timothy Takaro, a professor of Health Sciences at Simon Fraser University (SFU), has helped to answer this question. "In our study of more than 2,000 babies, we found that those more frequently exposed to cleaning products in their first few months of life had a significantly higher risk for asthma and other breathing problems by age three."

Some of the prime cleaning culprits, he says, were air fresheners, plug-in deodorizers, dusting sprays, and oven cleaners.

"We looked at the combined use of a wide array of products, not just each product in isolation," Takaro explains, "In so doing, we were able to identify the 'worst offenders' and to assess the impact of cumulative exposure on a child's asthma risk."

Bringing it all back home

For Takaro – whose training includes occupational and environmental medicine, public health, and toxicology – this study caps years of research into the factors contributing to asthma. In earlier work, he focused on understanding how tobacco smoke, pet dander, dust mites, and mould affect the condition.

The inspiration for the current study was sparked by Jaclyn Parks, a graduate student at SFU's Faculty of Health Sciences. Parks had a special interest in household contributors to asthma risk, and she approached Takaro with the idea of looking into the potential risks posed by cleaning products. "I was studying cleaning products in a class project around that time," Parks recalls. "Before that project, I had assumed there was strong regulation around these products, but I learned that this was not the case."

"Asthma is the most common chronic childhood disease and the primary reason why children miss school or end up in hospital, so this seemed like an important area to investigate," says Takaro. "There is evidence linking cleaning product exposure to asthma in adults, but we believe ours is the first study to look at exposure among infants."

Takaro took Parks on as a research trainee and they launched the project using data from the CHILD Cohort Study (CHILD) – one of the largest studies in the world to look in detail at how a baby's genes and environment interact to impact the development of asthma, allergies, obesity, and other chronic diseases. Nearly 3,500 Canadian children and their families are participating in CHILD and it is an "unprecedented, ongoing resource" that has collected more than 40 million data points, according to Takaro.

When CHILD babies were just a few months old, their parents completed questionnaires about the family's use of dozens of household products – everything from multipurpose cleaning sprays and toilet bowl cleaners to polishes and air fresheners. CHILD research teams also visited the families' homes to perform environmental assessments

and analyze the babies' exposure to dust; mould; furry pets; chemicals and cleaning products; cooking emissions; second-hand smoke; and air pollution in the surrounding neighbourhood. This in-depth home assessment was unprecedented; CHILD became the first study of its kind to analyze the home environment of such a large number of study participants in such detail.

Using this data, Takaro and Parks focused on data from 2,022 CHILD participants and examined their daily, weekly and monthly exposure to 26 types of household cleaners. They assigned a Frequency of Use (FUS) score to every participant by summing up the household usage patterns for each type of cleaner. "It's a cumulative score, so it doesn't tell you much about the individual products used. For example, a family using four products every day might have the same FUS as a family using eight products every month," Parks explains. The FUS scores served as a basis for grouping the families into three categories of exposure to cleaning products – low, moderate or high – and for assessing the risk of negative health outcomes as the FUS score increases.

Their research question was simple: To what extent might the level of exposure to these cleaning products, alone or in combination, impact the risk of a baby developing asthma by age three?

Trouble in the air

The answer to that simple question? "Enough to encourage change."

Their analyses, adjusting for other factors, found that babies with a high frequency of exposure to cleaning products had a 37% greater likelihood of being diagnosed with asthma by three years of age compared to babies with a low frequency of exposure. The babies from high-FUS homes also had a 35% higher likelihood of developing recurrent wheeze by the same age, and a 49% greater likelihood of having both recurrent wheeze and at least one allergic sensitization – a combination of conditions that makes a child more likely to develop asthma later on.

The analysis considered other factors known to impact the development of asthma, such as family history, geographical location, and early exposure to tobacco smoke. Parks says, "We sufficiently accounted for enough other factors that could possibly affect asthma development that we were confident the cleaning product relationship was real."

Poster (detail) by CHILD participant Mikaela (8 years old), from Vancouver, BC

But how exactly do cleaning products impact asthma risk?

Takaro doubts that overstimulation of the adaptive (specific, learned response) immune system can explain the effect: "We didn't find an association between the use of cleaning products and a risk of atopy (a heightened immune response to common allergens) alone. We think, instead, that the body's innate (general, rapid response) immune system is more likely involved, and that the chemicals in cleaning products may damage the cells lining the respiratory tract by triggering inflammatory pathways, leading to asthma and wheeze."

Exposure to cleaners may also cause changes to an infant's gut microbiome – the trillions of microbes that live in the human digestive tract – and this may also play a role, he added.

Another unexpected discovery: exposure to cleaners impacted girls more than boys. According to Takaro, some previous research already suggested that females are more inclined to have severe reactions to inflammatory exposures such as cigarette smoke. "There may be some differences in immune system tuning between the genders. This question calls for more research."

Babies may be especially vulnerable to airborne chemicals because their breathing rates are faster than adults. Also, they are frequently in contact with surfaces such as counters and floors, which can increase their exposure to chemicals in cleaning products. "There's also the fact that infants typically spend 80% to 90% of their time indoors," Takaro notes.

In addition to FUS scores, Takaro and Parks considered the effect of different product categories. They found that sprayed, fragranced, and disinfecting products carried the

greatest potential for harm, when used at a higher frequency. "We didn't see a strong or conclusive association with products that may be toxic but were rarely used, like drain cleaner," says Parks. "This may be partly explained by the fact that there were not enough people using drain cleaner on a daily or weekly basis to make a strong statistical comparison to those who used it less frequently."

Scents don't make sense

The study's findings may prompt some families to scale back on their use of cleaning products.

"Unfortunately, we can't tell parents which products are safe, because Canadian regulations don't require manufacturers to disclose ingredients that account for less than 2% of the product's total volume," says Takaro, "and for some compounds, much smaller concentrations could still potentially cause harm."

What to do, then?

"Whenever possible, get back to basics," Parks advises. For simple cleaning tasks, like wiping off a countertop after you made lunch: "There's no need to go beyond soap and water. Don't pull out the big guns unless you really need them."

Of course, soap and water won't go far when it comes to cleaning a grime-coated oven. For such heavy cleaning tasks, Parks suggests that parents keep young children out of the area while cleaning, and ventilate the room during and after cleaning before letting children back in. Similarly, if a cleaning job requires more than one product "as you might expect when cleaning a bathroom, for example," says Parks, she recommends using cleaners sequentially, rather than simultaneously. "Mixing products can create new 'secondary' chemicals and additional toxicity."

Other precautions: avoid sprays and scented products whenever posisble. "There's really no reason to use air freshener: it just masks other underlying problems, like the presence of bacteria or mildew, or inadequate ventilation that should be fixed to improve indoor air quality," Parks says. "We believe the smell of a clean home is no smell at all."

Cleaning during COVID-19

The *Canadian Medical Association Journal* (*CMAJ*) published the study in February 2020, and the researchers received over 300 requests for interviews within a few days of publication. "It was exciting that media in Australia and India were talking about our work," says Parks, who co-wrote the paper while working on her master's degree.

Then COVID-19 rolled in and hygienic practices assumed an entirely new level of importance. Suddenly, everyone was advised to clean, clean, clean: wipe down groceries, disinfect doorknobs, wash hands, and the more the better.

Recognizing the tension between the insights of their study and the demands of pandemic protocols, Takaro and Parks wrote a follow-up letter to CMAJ in which they acknowledged that the COVID-19 crisis "warrants the use of disinfectants at an increased frequency." They encouraged parents to balance the need to prevent the spread of the virus by using disinfection practices while limiting their child's exposure to cleaning products.

To minimize risks from the use of disinfectants, they advised parents to "first wash a surface with soap and water to remove as many pathogens as possible, then use an appropriately diluted amount of disinfectant to kill the remainder."

For settings like schools and workplaces, and in homes of those who are frequently interacting with other members of the public, the researchers recommended using disinfectants on high-touch surfaces where virus-containing droplets could settle. "This is likely more important in areas where community transmission is evident," adds Parks.

"We remind parents that disinfectants can be used in an appropriate context and applied in a responsible manner," they wrote, while also championing physical distancing and other guidelines to reduce exposure, along with frequent hand washing with soap and water, and wearing masks.

"Heavy disinfection alone is not a substitute for following recommended public health measures to prevent transmission of the virus," says Parks. "But it's an additional precaution that can be done safely and responsibly – with our kids' health in mind."

"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.

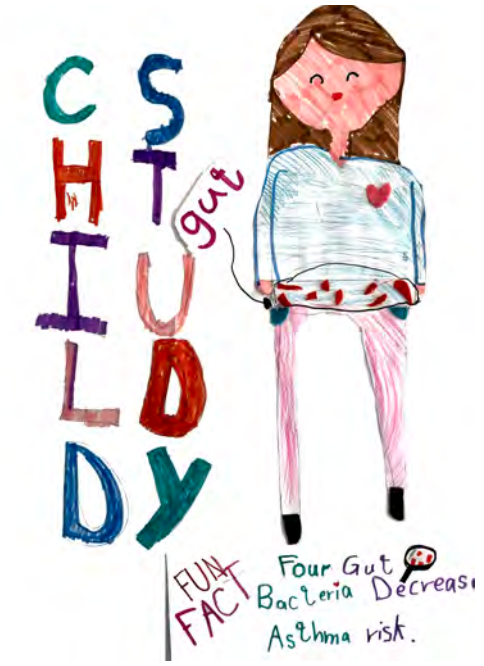
The researchers also looked at individual-level data from the more than 2,600 Canadian children with antibiotic use data participating in the CHILD Cohort Study (CHILD) – a national birth cohort study that is determining how an infant's genes, environment, and early-life exposures influence health and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

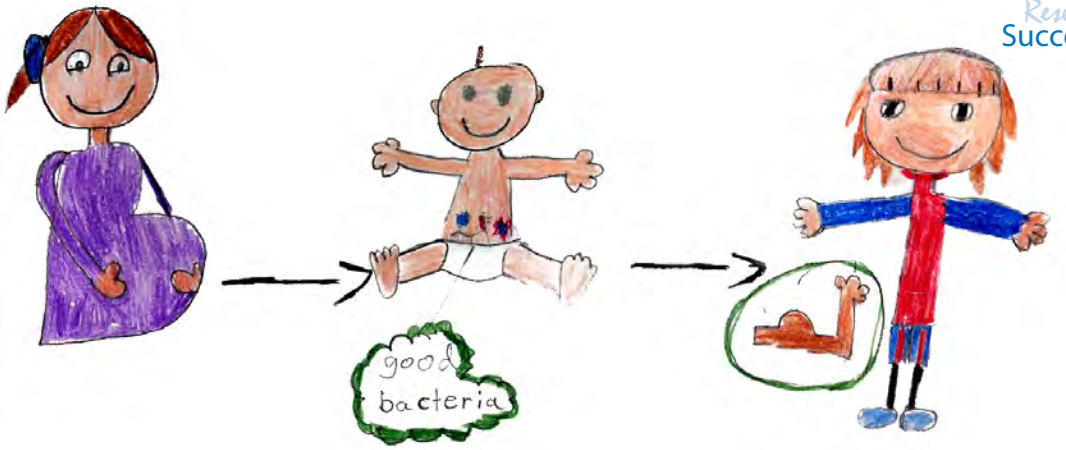
The gut "sits in the middle"

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!"

CHILD researchers, staff and Study kids at a June 2018 celebration in Toronto, ON

Research Success Stories

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