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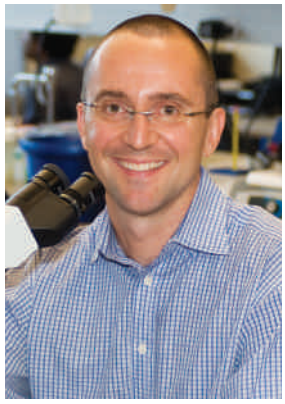
Anti-Asthma Squad: Four Gut Bacteria Help Protect Kids from Developing Asthma

If you were holding a baby in your arms and wondered if an asthma diagnosis could lay in its future, the baby's diaper would likely be the last place you would think to look for an answer. But think again: researchers at The University of British Columbia (UBC) have traced a solid line between specific bacteria in an infant's gut and the risk of developing asthma.

Dr. Brett Finlay, Professor
The University of British Columbia



Dr. Stuart Turvey, Professor
The University of British Columbia

Dr. Brett Finlay, a microbiologist and a Peter Wall Distinguished Professor at UBC, and Dr. Stuart Turvey, a pediatric immunologist at BC Children's Hospital who holds the Aubrey J. Tingle Professorship in pediatric immunology, led the research that discovered four types of gut bacteria play a critical role in protecting children against asthma. More specifically, infants with low levels of these bacteria at the age of three months had a significantly higher risk of asthma, even if their bacteria levels normalized later. "It points to a window in the first 100 days or so of life, when disruptions in the normal composition of bacteria in the gut can derail the immune system and lead to asthma down the road," says Dr. Finlay.

The importance of "flavour"

The bacteria are called *Faecalibacterium, Lachnospira, Veillonella* and *Rothia*—tongue-twisting names that Drs Finlay and Turvey have collapsed into the acronym FLVR, pronounced "flavour." It is not yet clear why some infants have low levels of FLVR bacteria, but finding out could prove crucial to predicting which children are at risk for asthma, and perhaps even for preventing the condition from developing in the first place. "My guess is that certain factors known to disrupt normal gut bacterial colonization, such as caesarean-section delivery and exposure to antibiotics, might play a role," says Dr. Finlay.

Their research, which was funded by the Canadian Institutes of Health Research (CIHR) and published in the journal *Science Translational Medicine* in September 2015, quickly grabbed worldwide attention, generating over 400 headline stories within 24 hours. The research team, including co-first authors Dr. Marie-Claire Arrieta and Leah Stiemsma, juggled 90 interviews from international media outlets in countries as far-flung as Korea and Brazil. Dr. Turvey's mother saw a report of the Canadian scientific discovery on the local 6 p.m. news—at her home in Sydney, Australia.

"This is the first study to identify some of the specific microbes that influence asthma," says Dr. Turvey. "We received emails from families affected by asthma thanking us for our work." The outpouring of gratitude attests to the burden asthma places on families. "I think we sometimes underestimate this," he admits. "People are eager for anything that might help—even bacteria."

The smoking gun

We used to think of bacteria as our enemies, and early antibiotic researchers waged war against them. It's only in recent years that scientists have recognized the importance of "friendly germs"—bacteria that keep our digestive system in working order and may keep a host of ailments at bay. The idea that we can happily coexist with germs has kindled researchers' interest in the makeup of our microbiome—the trillions of bacteria, viruses, fungi and other microorganisms that inhabit our body.

The more scientists delve into the microbiome, the more they find: we now know that imbalances in the microbiome can predispose people to obesity, metabolic disorders, urinary tract infections, and eczema, among other conditions.

The digestive system may seem like an unusual place to search for asthma clues, but the UBC team had good reason to look there. Many of the factors linked to asthma—like caesarean-section delivery, formula feeding or early life exposure to antibiotics—have to do with bacteria, according to Dr. Turvey. For example: "A caesarean section is a sterile procedure and the baby misses out on being exposed to the invisible, and possibly helpful, microbes in the mom's birth canal."

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"We also know that the microbiome has a bearing on immune system function, and asthma involves immune disruption," adds Dr. Finlay. "There have been a number of 'smoking guns' to suggest that microbes might be involved in asthma development, but no experiments to prove it. That's the gap we were able to fill."

Tracking down the right bugs

In their research, Drs Finlay and Turvey, both AllerGen investigators, used data from 319 children enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) Study, a unique birth cohort study that is tracking 3,500 Canadian children and their families from pregnancy to the age of five in an attempt to unearth the root causes of allergy, asthma and other chronic diseases. Dr. Turvey leads the Vancouver arm of the CHILD Study, which is funded by AllerGen and CIHR. Other CHILD Study sites are located in Winnipeg, Edmonton and Toronto.

Using stool samples collected from the children at three months and again at one year of age, the research team pieced together a picture of the babies' gut environments and the bacteria living there. They also assessed the children for early signs of allergies and asthma during clinical check-ups at ages one and three years.

The connection between gut bacteria and asthma risk did not leap out immediately; it was only when the researchers dug down to the level of specific bacterial genres that the link became evident. Children with low levels of FLVR at three months of age were more likely to wheeze and to have positive allergy skin tests (both are telltale signs of future asthma) at the age of one

year, even if their FLVR levels had become normal by then. On the flip side, children with no signs of asthma at one year of age had high levels of FLVR bacteria in their three-month stool.

And there was more. The babies who went on to develop asthma had higher or lower levels of certain bacterial by-products in their urine, suggesting that these chemicals might induce the immune system to either trigger or ward off asthma.

To confirm the significance of the FLVR bacteria, the researchers conducted a separate study in mice. They bred "germ-free" mice without any gut bacteria and transferred stool from three-month old babies who were FLVR-deficient into the mice. They found that the animals developed inflamed lungs—an early signal of asthma. However, if the researchers deliberately supplemented the mice with the missing FLVR bacteria, inflammation decreased and the risk for asthma disappeared.

Although Dr. Finlay calls the study's findings "preliminary," the research seems to support the idea that we are making our environment too clean, a theory known as the "hygiene hypothesis." "We have done a great job getting rid of microbes that cause infectious diseases, which were the leading cause of death a century ago, but we may have gone too far," he warns. In other words, "we may be living too cleanly, which could be contributing to the rise in asthma and allergies. We need to push the pendulum back toward a middle ground to achieve a balance between hygiene and helpful environmental exposures."

Opening the door

The FLVR discovery could profoundly impact medical practice. It opens up the possibility of flagging children most at risk for developing asthma by testing their microbiome in the first three months of life. Those children could be monitored closely and treated quickly if they showed signs of asthma. It also opens the door to developing FLVR probiotic treatments to prevent asthma in the first place.

Before probiotic therapies for infants become a reality, however, researchers will need to spend more time at the lab bench. "We need to confirm our results in larger groups of children and in different parts of the world," says Dr. Turvey. "We also need to make sure that any new probiotic supplements or treatments are safe for babies," he notes. All this could take several years, but "at least we've opened the door."

In the meantime, the Finlay and Turvey labs are forging ahead in their quest to fill in the remaining knowledge gaps. Dr. Finlay's team is planning follow-up studies in Ecuador to find out whether or not the FLVR phenomenon extends to children who grow up in a very different environment, and UBC has filed a patent for the FLVR discovery that could lead to a new therapy down the road.

For the time being, parents intent on keeping their infants away from germs might want to reconsider their position, says Dr. Finlay. "There's such a thing as good dirt, and we shouldn't fear it so much."