

“The ability to develop objective markers that accurately identify those children who truly will respond to inhaled steroids will reduce the amount of medication that is unnecessarily prescribed and potentially harmful,” states Dr. Subbarao.



When is Your Child's Wheeze a Sign of Asthma? Canadian Researchers Establish New Diagnostic Tests for Infants and Young Children

This is the story of a Toronto pediatrician and her drive to find cutting-edge tests for lung function and airway inflammation that could be used to objectively identify infants and young children with asthma. Thanks to the efforts of Dr. Padmaja Subbarao and her team, Canada is poised to become a world leader in preschool asthma research.



Dr. Padmaja Subbarao, Clinician-Scientist, The Hospital for Sick Children and Assistant Professor, University of Toronto

Wheezing Kids and the Need for Non-Invasive Diagnostic Tests

Wheezing is generally described as a chesty, whistling sound that is heard when a child breathes out and sometimes also when they breathe in. In children under the age of six, episodes of wheezing are exceedingly common. In fact, nearly half of all children have experienced a bout of wheezing. There are a wide variety of underlying causes for childhood wheezing, including lung infection that develops from viruses like the common cold, being born with abnormally small airways, cystic fibrosis and, of course, asthma.

Dr. Subbarao is a pediatric respirologist, or more simply, a child lung doctor, who was frustrated that she and her fellow physicians didn't have handy diagnostic tests to determine which wheezing children under the age of six have asthma and which don't. They relied solely on X-rays and clinical symptoms in order to make their diagnoses.

Currently, most children who experience wheeze are treated with escalating doses of powerful inhaled steroids. What troubles Dr. Subbarao is the fact that only 15% of these children have allergic asthma that responds to such drugs. "The ability

to develop objective markers that accurately identify those children who truly will respond to inhaled steroids will reduce the amount of medication that is unnecessarily prescribed and potentially harmful," states Dr. Subbarao.

Around the age of six, children are typically able to perform the traditional lung function test, which involves blowing into a tube. Children younger than four years of age usually haven't mastered how to blow out through their mouths. If you have ever watched a young child try to blow out candles on a birthday cake but cannot, "It's the same reflex. They want to be able to do it, but they don't know how," explains Dr. Subbarao.

The problem with waiting until a child is capable of performing the traditional lung function diagnostic test is that, in the meantime, the child's airways are potentially being damaged by asthma if the child in fact has the disease. The latest research demonstrates that the disease develops early in a child's life, perhaps even in the womb. Thus, the earlier the diagnosis can be made, the better. This could mean improved control and management of the disease, which will hopefully result in not only fewer hospital admissions and missed school days, but also better quality of life, less anxiety and less time

Success Stories: Innovation from cell to society

away from work for parents. According to the Asthma Society of Canada, this disease is currently the leading reason for children missing school, as well as for hospital emergency room visits.

Based on the limitations of current diagnostics tools, Dr. Subbarao set out to develop cutting-edge tests for lung function and airway inflammation that could be used to objectively identify infants and young children with asthma. The tests needed to be safe and comfortable for children to undergo; otherwise they too would be ineffective. "My work in this area is really born out of a clinical need," says Dr. Subbarao.

The data generated by the CHILD Study will offer insights into how allergic diseases get their start. It should be noted that this data will be clinically useful for research in every area of paediatric respiratory disease, such as cystic fibrosis, congenital lung disorder and interstitial lung disease....

Canada's First Infant Lung Function Laboratory

With funding from AllerGen NCE and The Hospital for Sick Children in Toronto, Canada now has an infant lung function laboratory. This is a major accomplishment, since there are only a few centres in the world that do specialized testing on infants due to the extensive training required of both the physicians and technologists involved.

Dr. Subbarao and her team, Drs Malcolm Sears (McMaster University; St. Joseph's Healthcare); Martin Post (University of Toronto; The Hospital for Sick Children Research Institute); Felix Ratjen (University of Toronto; The Hospital for Sick Children); Hartmut Grasemann (University of Toronto; The Hospital for Sick Children; The Hospital for Sick Children Research Institute); Dean Befus (University of Alberta); and Darryl Adamko (University of Saskatchewan) are working on multiple tests to measure lung function and airway inflammation that involve both developing new and testing existing technologies.

The big question to be answered is whether or not these

tests are able to accurately predict asthma in infants and children before they are able to perform the standard lung function test by blowing into a tube. While research is ongoing, Dr. Subbarao and her dedicated team have thus far established that lung function tests can be done on children as young as three months of age. It causes them no discomfort. In fact, she notes that they are able to sleep through the test.

The team has also looked at and ruled out *Exhaled Breath Condensate* as a useful test for diagnosing preschool asthma; a surprising result given the buzz about this new test in lung research circles. Dr. Subbarao explains that researchers expected



© DMITRY NAIMOV / FOTOLIA.COM

to find at least one correlation between what is breathed out and airway inflammation measured in the sputum of asthmatics as a result of chance or statistical error. However, there wasn't even one correlation among the fifty different parameters measured. She concluded that "this test was extremely unimpressive."

While they were disappointed with the *Exhaled Breath Condensate Test*, the team has been impressed by results from the *Multiple Breath Wash Out Test*, which is a lung function test developed in Sweden by paediatric respirologist, Dr. Per Gustafsson. This test measures how well the lungs perform in breathing and clearing gases. If a person has airway obstruction resulting from inflamed airways due to asthma, it is hard for them to get air in and out of their lungs.

Performing this test involves wearing a face mask and breathing in a precise mixture of gases while hooked up to a machine that measures the concentration of the different gases exhaled. "It's an amazing technology because it can be applied

to infants as well as to adults,” says Dr. Subbarao. What is remarkable about this test is its ability to detect lung disease in early life. Originating from research that has been done on children living with cystic fibrosis, the test is very precise in that it has very tight cut-off markers for what is normal and what is abnormal lung function.

Dr. Subbarao describes the *Multiple Breath Wash Out* test as “leading-edge technology.” The laboratory that she helped establish is the only one in North America that has this test available. “With respect to the technology development that we have done here in Toronto, this is the jewel in our crown,” she says.

What’s Next for Our Infant Lung Function Laboratory?

Once Dr. Subbarao and her team have confirmed which tests have predictive value and have perfected the techniques for using these tests, they will be put to use as part of the *Canadian Healthy Infant Longitudinal Development (CHILD) Study*. This multidisciplinary study of 5,000 Canadian children, enrolled from pre-birth and followed for five years, is by far Canada’s biggest asthma and allergy focused birth cohort study. It will allow this team to administer the tests easily and effectively so that they may diagnose or rule out asthma in early childhood.

Dr. Subbarao is excited that the CHILD Study is collecting data on children with healthy lungs, in addition to data on children diagnosed with asthma. In terms of lung health, control data from healthy subjects has never been collected in Canada before, so researchers don’t yet know what is *normal* for Canadian babies and young children.

The data generated by the CHILD Study will offer insights into how allergic diseases get their start. It should be noted that this data will be clinically useful for research in every area of paediatric respiratory disease, such as cystic fibrosis, congenital lung disorder and interstitial lung disease — not only the development of asthma and allergy. “This data will be important for Canada and the rest of the world,” says Dr. Subbarao.

The lung function and airway inflammation tests that Dr. Subbarao and her team are establishing could soon be used to not only diagnose asthma earlier and in mild cases, but also to serve as a vital tool in disease management. “Ultimately, we hope that a combination of these lung function measures,

once tested within the CHILD Study, will help us to diagnose infant asthma,” says Dr. Subbarao.

These new tests will also become important for future drug trials. The *Multiple Breath Wash Out Test* has already been used in the cystic fibrosis population and has been shown to reduce the number of child subjects needed for a study. The result is that researchers can now do *proof of concept* studies for new therapeutics with increased efficiency. Previously, 200+ children were required to perform a study in order to show that a drug has treatment effect. Now, because the *Multiple Breath Wash Out* test is very sensitive, researchers can measure as few as 17 children to show therapeutic effect for a new drug. This leads to tremendous reductions in cost as well as the potential to speed up the rate at which a new drug can reach the market and be used by Canadians.

Additionally, these new tests could also help researchers develop new therapies for non-asthma wheezing. “We have very little to offer those kids in our emergency rooms that have wheeze, but are not necessarily asthmatic,” says Dr. Subbarao.

The Vital Importance of AllerGen NCE Funding

With funding from AllerGen NCE, Canada is one of the few countries in the world to have an infant lung function laboratory. “AllerGen plays a very significant role in trying to understand and reduce the burden of allergic diseases in Canada,” says Dr. Subbarao.

AllerGen NCE funding has made cutting-edge techniques for measuring infant lung function and airway inflammation available in Canada and more importantly, has enabled validation of these new techniques on the Canadian population. The payoffs will no doubt be significant — reducing the financial burden on the health system and reducing the disease burden borne by those living with asthma. These tests will be instrumental tools for CHILD Study researchers, helping them in their quest to understand the origins of allergic diseases. They are also set to become useful tools for physicians in diagnosing and managing preschool asthma, not to mention a host of other lung diseases. In addition, these techniques are extremely important to the development of new therapeutic treatments and for use in future drug trials. 