Homogeneous tuberculosis treatment ineffective in children, researchers find

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The realization of medically treating different children uniquely may start with one of the deadliest diseases in existence: tuberculosis.

New findings by UT Southwestern Medical Center researchers indicate that the type of medications and the dosage routinely used to treat children with the disease should be individualized to each young patient in order to be effective.

The findings, available online and in the February issue of *Antimicrobial Agents and* Chemotherapy, show that currently recommended doses are much too low and that a child's weight, age and medical history are among a myriad of factors that can affect his or her response to a particular drug used to combat the Mycobacterium tuberculosis bacterium, which causes the disease.

"Children are growing and changing and, unlike in adults, Mycobacterium tuberculosis manifests itself in children as many different diseases, causing problems all over the body," said Dr. Tawanda Gumbo, associate professor of internal medicine at UT Southwestern and the study's lead author. "Since their immune systems are not yet fully developed, you also have to take into consideration whether a particular drug will reach the part of the body affected by the disease.

"If you aggregate all these factors – age, weight, medical history, disease process – it's pretty clear that you need to treat each child differently

instead of following the standard dosing guidelines."

About one-third of the world's population is infected with Mycobacterium tuberculosis and 2 million people die from the disease each year. TB, the leading cause of death among people infected with HIV/AIDS, kills more people than any other disease caused by a single infectious agent, according to the National Institutes of Health. Treatment usually lasts six to 12 months and includes a combination of drugs administered simultaneously, in hopes of preventing drug resistance.

For the study, the researchers virtually simulated clinical trials involving 10,000 patients who are 10 years old or younger. The computer simulation factored in pharmacokinetics (how a body handles a drug based on heterogeneous factors) to determine how likely a dose of a given drug is to kill TB. The children were grouped into three groups: fast acetylators, meaning their bodies metabolize the drugs quickly; children ages 1 to 10 who are slow acetylators; and infants who are slow acetylators.

Dr. Gumbo's team found that the drug concentrations typically used to treat children with TB are too low and that children respond differently to the standardized medication depending partly on their age and how quickly their bodies metabolize the drug.

"Despite the desire for standardized therapy, our findings support the long-held notion that there is no 'average' or 'standard' child. It is safe to assume that with 2.2 billion children worldwide, there will be 2.2 billion different regimens needed to effectively treat tuberculosis," Dr. Gumbo said.

He said the importance of the findings is that they can be applied to many other infections, including methicillin-resistant-Staphylococcus

aureus, or MRSA.

"This is the future, even for adults," Dr. Gumbo said. "Being able to individualize what drug someone gets and what dose – this is the future of medicine."

Dr. Gumbo's research is funded by a 2007 NIH Director's New Innovator Award, which supports bold ideas from some of the nation's most innovative early-career scientists.

Dr. Jotam Pasipanodya, research scientist in internal medicine at UT Southwestern, and researchers from the University of KwaZulu-Natal, the Howard Hughes Medical Institute, and the Kwa-Zulu Natal Research Institute for Tuberculosis and HIV in South Africa also contributed to the study.

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