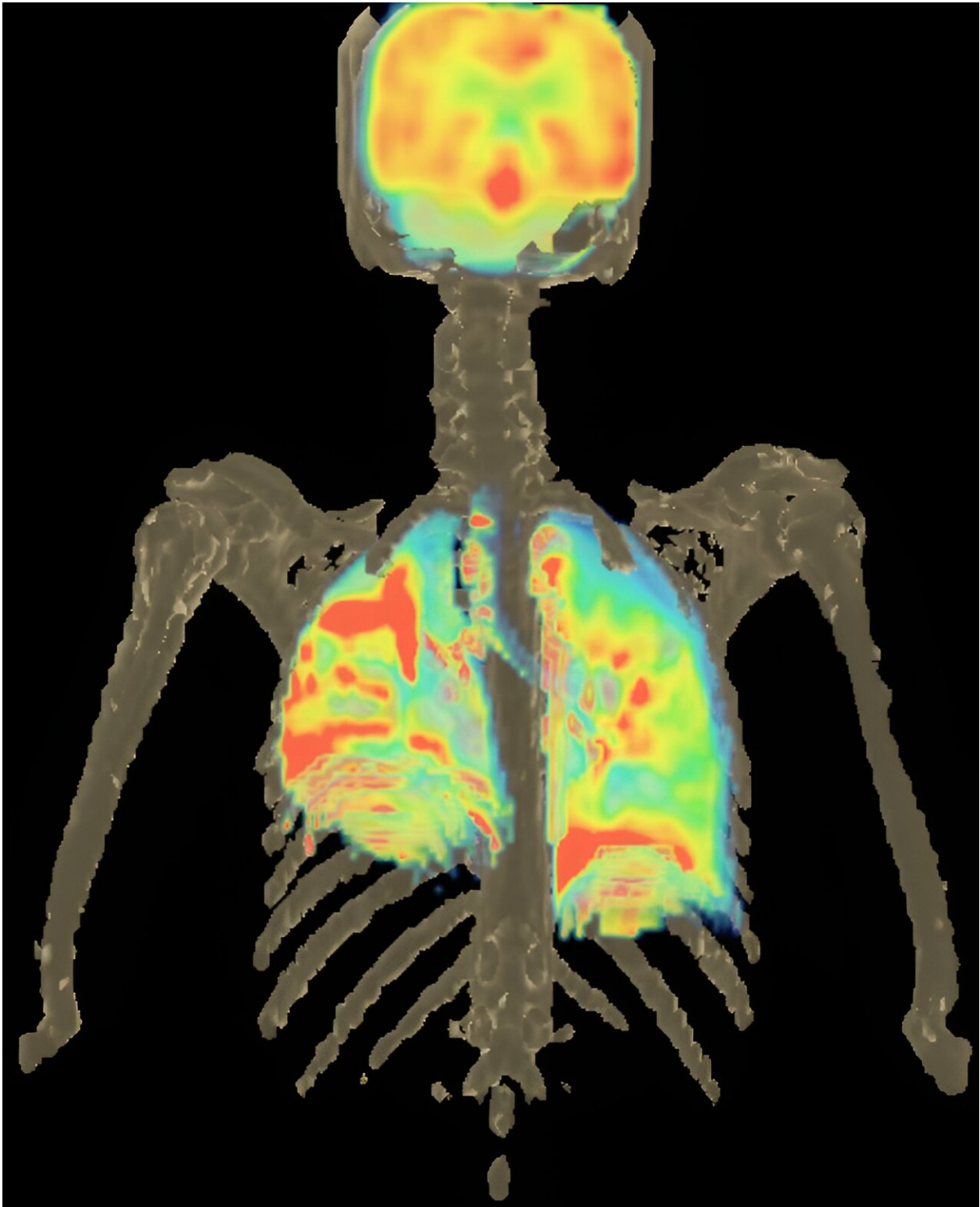


Researchers report potential new treatment regimens for multidrug-resistant TB meningitis

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18F-Pretomanid exposure in brain and lung tissues of a patient with active tuberculosis. Credit: Sanjay Jain Lab

In a preliminary study with a small number of humans, rabbits and mice, researchers at Johns Hopkins Children's Center say they have developed four new regimens that have the potential to treat and save the lives of people with multidrug-resistant (MDR) tuberculous (TB) meningitis.

While TB meningitis—which affects the brain and spine—is extremely rare in the United States, worldwide it is believed to be the deadliest form of TB.

In a [report](#) published Aug. 14 in *Nature Communications*, the investigators present the regimens, mainly composed of antibiotics already approved by the U.S. Food and Drug Administration (FDA) for other uses, or antibiotics currently in clinical trials.

Study investigators say the regimens could be readily evaluated in new clinical studies, or used to treat people with MDR-TB meningitis on a case-by-case basis now.

According to the World Health Organization, tuberculosis remains a global public health threat, with the largest number of cases occurring in the Southeast Asian region and Africa, and is a leading killer by a single infectious agent, the tubercle bacillus.

There are no FDA-approved antibiotic treatments specifically effective for tuberculous meningitis, although [antibiotic treatments](#) developed for TB of the lungs are widely available.

A previous Johns Hopkins Children's Center study led by Sanjay Jain, M.D., senior author of the new study and director of the Johns Hopkins Center for Infection and Inflammation Imaging Research, showed that the FDA-approved regimen of three antibiotics currently used for

treating drug-resistant pulmonary TB—bedaquiline, pretomanid and linezolid (BPaL)—is not effective in treating TB meningitis, because bedaquiline and linezolid can't efficiently cross the [blood-brain barrier](#)—a network of cells that prevents the entry of germs and toxins into the brain.

The new study used [positron emission tomography](#) (PET) scan and CT scan technology on people, rabbits and mice to show how different antibiotics penetrate the brain and other areas of the body, says Jain, who is also a pediatric infectious diseases specialist at Johns Hopkins Children's Center.

For the new experiments, researchers first created a chemically identical and scan-friendly version of the antibiotic pretomanid, and conducted a whole-body study in eight people: six healthy volunteers and two patients newly diagnosed with pulmonary TB.

Using PET and CT imaging, researchers measured the antibiotic's penetration into the brain and [lung tissue](#), and found that pretomanid penetrated the brain more than two times better than the lungs of all human subjects. Pretomanid levels in the cerebrospinal fluid (CSF) were also different from those in the brain.

"We have found that CSF levels of antibiotics often have no relation to those in the brain," says Xueyi Chen, M.D., one of the study's first authors and a pediatric infectious diseases fellow at the Johns Hopkins University School of Medicine.

Next, using PET imaging, the researchers tested four different antibiotics (chemically identical and imageable versions) active against MDR-TB—pretomanid, sutezolid, linezolid and bedaquiline—and their penetration into the lung and brain tissues in mouse and rabbit models of TB meningitis.

All four antibiotics distributed well in the body, but with significantly different brain and lung tissue penetration. While pretomanid levels were significantly higher in the brain versus lung tissue, sutezolid, linezolid and bedaquiline had at least three times higher levels in lung tissue—with bedaquiline demonstrating levels almost tenfold higher than in the brain.

"Interestingly, pretomanid brain levels were double the amount in the plasma. In contrast, while bedaquiline brain levels were almost one-fifth the plasma levels, the lung levels were double the amount in the plasma. This preferential accumulation of different antibiotics in brain or lung tissues is very important, and explains why certain antibiotics are highly effective in the lungs, but not in the brain and vice versa," says Jain.

Researchers next created computer models that parallel and measure how drugs behave in living systems, so called pharmacokinetics, for pretomanid, sutezolid, linezolid and bedaquiline. Mathematical simulations based on the models were then used to predict which tissue exposures and doses would be necessary to attain therapeutic brain penetration of each antibiotic.

Only pretomanid achieved therapeutic brain tissue exposures at the standard human oral dosing. Even at a dose four times the standard human oral dose, bedaquiline brain tissue exposures were predicted to be only one-third of the target levels.

Researchers found that the three pretomanid-based multidrug regimens—BPa50LZ (bedaquiline, pretomanid, linezolid, pyrazinamide), Pa100LZ (pretomanid, linezolid, pyrazinamide), and Pa50LMxZ, (pretomanid, linezolid, moxifloxacin, pyrazinamide)—were highly effective in treating TB meningitis in animal models when administered at human equivalent dosing.

Each regimen's ability to kill bacteria in the brain was several magnitudes higher than both the standard TB treatment (R10HZ) and the BPaL regimen (BPa50L).

Since MDR-TB strains can also be resistant to pyrazinamide, researchers developed a fourth regimen, one without pyrazinamide: Pa100SMx (pretomanid, sutezolid, moxifloxacin). They found it was as effective as the first-line standard TB treatment, and 10 times better at reducing the bacterial burden in the brain than the BPaL regimen.

Investigators cautioned that their experiments were limited by the small quantities of the imageable version of antibiotics used per subject. However, several studies support that dosing with small quantities of a drug are a reliable predictor of a drug's bodily distribution.

More information: *Nature Communications* (2024).
www.nature.com/articles/41467-024-50989-4

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