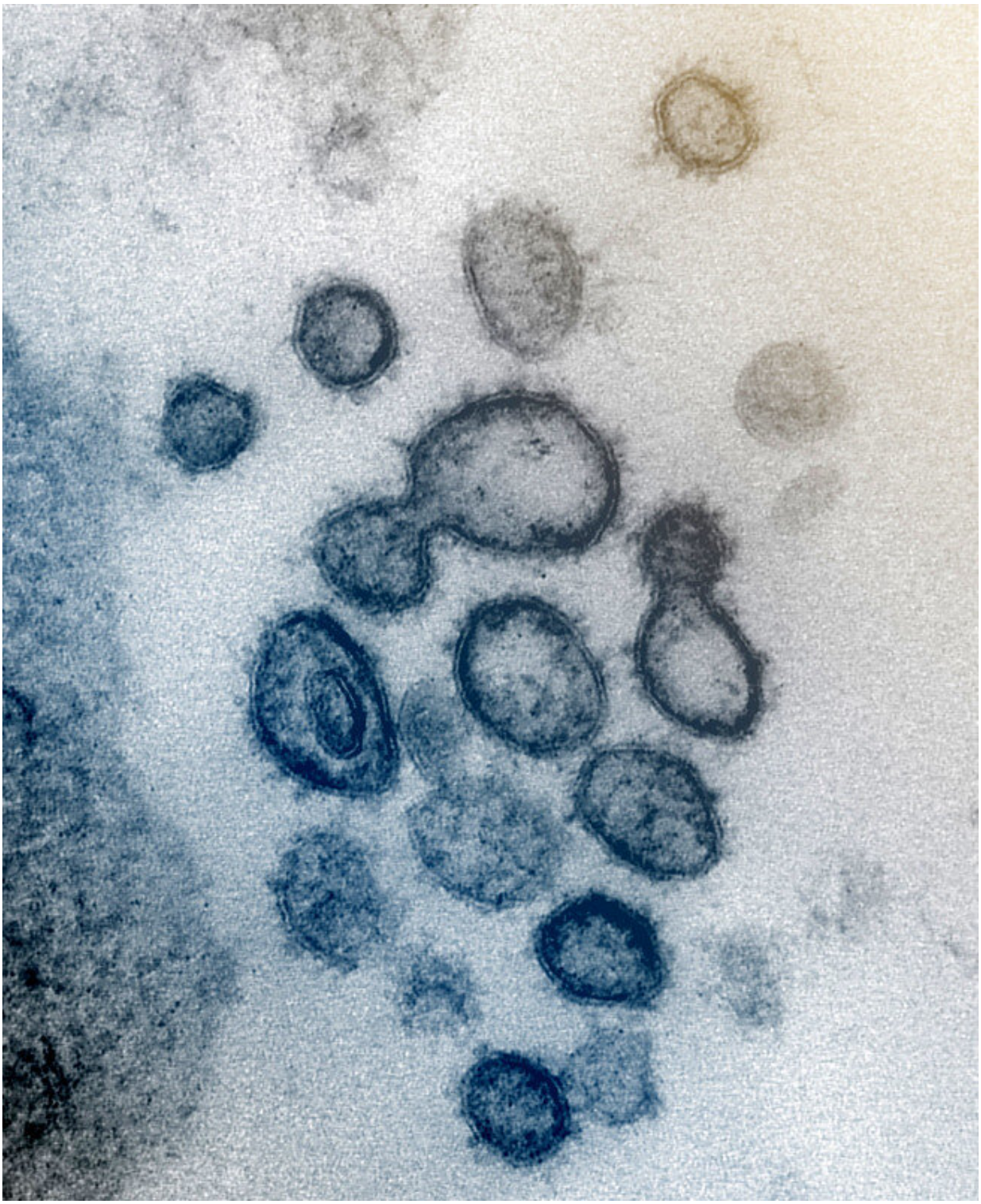
Why does COVID-19 seem to spare children? New study offers an answer

November 13 2020



This transmission electron microscope image shows SARS-CoV-2 -- also known as 2019-nCoV, the virus that causes COVID-19 -- isolated from a patient in the US. Virus particles are shown emerging from the surface of cells cultured in the

lab. The spikes on the outer edge of the virus particles give coronaviruses their name, crown-like. Credit: NIAID-RML

Researchers at Vanderbilt University Medical Center (VUMC) and their colleagues have determined a key factor as to why COVID-19 appears to infect and sicken adults and older people preferentially while seeming to spare younger children.

Children have lower levels of an enzyme/co-receptor that SARS-CoV-2, the RNA virus that causes COVID-19, needs to invade airway epithelial cells in the lung.

The findings, published today in the *Journal of Clinical Investigation,* support efforts to block the enzyme to potentially treat or prevent COVID-19 in older people.

"Our study provides a biologic rationale for why particularly infants and very young children seem to be less likely to either get infected or to have severe disease symptoms," said Jennifer Sucre, MD, assistant professor of Pediatrics (Neonatology), who led the research with Jonathan Kropski, MD, assistant professor of Medicine.

Sucre and Kropski are co-corresponding authors of the paper. Bryce Schuler, MD, Ph.D., a resident in Pediatrics and Genetics at VUMC and postdoctoral fellow in the Vanderbilt Stimulating Access to Research in Residency program, is the paper's first author.

There is still much to learn about SARS-CoV-2. But this much is known: After a viral particle is inhaled into the lungs, protein "spikes" that stick out like nail studs in a soccer ball attach to ACE2, a receptor on the surfaces of certain lung cells.

A cellular enzyme called TMPRSS2 chops up the spike protein, enabling the virus to fuse into the cell membrane and "break into" the cell. Once inside, the virus hijacks the cell's genetic machinery to make copies of its RNA.

Sucre and Kropski, who have collaborated since 2016 on studies of lung diseases in premature infants and adults, wondered if TMPRSS2 had something to do with the greater severity of COVID-19 symptoms observed in older people compared to children.

"Our research has always focused on understanding lung development and how infant lungs differ from adult lungs in their vulnerability to injury," Sucre said. "In this study we actually took the opposite approach, and were able to see how the developing lung by its differences is protected from SARS-CoV-2 infection."

The researchers were well equipped to begin such a study. As members of the international Human Cell Atlas (HCA) Lung Biological Network, they and their colleagues had built a dataset on lung development in the mouse using a technique called single-cell RNA-sequencing.

The technique can detect the expression of genes in individual cells of tissues such as the lung. In this way the researchers were able to track the expression of genes known to be involved in the body's response to COVID-19 over time.

They found that while the gene for ACE2 was expressed at low levels in the mouse lung, "TMPRSS2 stood out as having a really striking trajectory of increased expression during development," Schuler said.

With the help of VUMC pathologists, the researchers obtained and analyzed human lung specimens collected from donors of different ages, and confirmed a similar trajectory in TMPRSS2 expression to what

they'd found in mice.

"What we found is that expression of (TMPRSS2) goes up significantly with aging, and we see that at the level of the gene and at the level of the protein," Sucre said. "We see a lot more TMPRSS2 in older individuals, in both humans and mice."

The researchers also used fluorescent probes to analyze autopsy specimens from three patients who died of COVID-19, and found the virus in three types of cells that express TMPRSS2.

TMPRSS2 is well known for its role in the development of prostate cancer. Drugs that block the enzyme and which have been approved for the treatment of advanced prostate cancer currently are being tested clinically as potential treatments for COVID-19.

The new findings reported today support further investigation.

"We do think TMPRSS2 could be an attractive target both in treatment and potentially as a prophylaxis for (preventing infection in) people at high risk of COVID exposure," Sucre said.

More information: Bryce A. Schuler et al, Age-determined expression of priming protease TMPRSS2 and localization of SARS-CoV-2 in lung epithelium, *Journal of Clinical Investigation* (2020). DOI: 10.1172/JCI140766

Provided by Vanderbilt University Medical Center

children-1.html