

# Gene variant and environment can boost severity of respiratory syncytial virus

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A particular genetic mutation combined with an urban environment increases the risk of severe disease in children infected with respiratory syncytial virus (RSV), an international team of investigators has found.

RSV infects half of the infants in the world every year, and 1 percent to 2 percent of infected infants are hospitalized for severe disease.

The study, reported in the *Journal of Clinical Investigation*, identifies a specific sub-population of [children](#) who are more likely to be hospitalized because of RSV infection, said Fernando Polack, M.D., Cesar Milstein Professor of Pediatrics at Vanderbilt and senior author of the report.

The findings support further studies directed at understanding how these children respond to RSV infection and discovering strategies to reduce their risk of severe disease, said Polack, who also directs Fundación INFANT in Buenos Aires, Argentina.

"This sub-population of children contributes to a significant number of the hospitalizations due to RSV, which is not trivial," Polack said.

Polack and his colleagues studied two independent populations of infants with bronchiolitis to explore the hypothesis that interactions between the environment and genetic variants in TLR4—a receptor that activates the innate immune response—modulate RSV disease severity.

They found that a particular genetic change in TLR4 was associated with more severe disease in children from urban middle-class families, but was associated with milder disease in children living in rural areas.

Urban children with the mutation were eight times more likely to be hospitalized with RSV infection compared to their neighbors without the mutation. Their risk for hospitalization may be similar to that for extremely premature babies, a highly vulnerable population for RSV disease.

The TLR4 mutation emerged as a protective variant at a time when humans had heavy exposure to environmental bacteria and other pathogens, Polack explained. It appears to play this protective role in children living on farms or in low-income populations in developing countries.

In cities with "clean water and a vacuum cleaner in every home, the mutation behaves completely differently," Polack said. Urban children with the mutation respond to RSV infection with an allergic response in the lungs. The children have high levels of the cytokine interleukin-4 and low levels of interferon-gamma in respiratory secretions, the researchers found.

Previous studies demonstrated that children with the TLR4 mutation—about 10 percent of children in the United States—may not be protected by palivizumab, the only medication approved to prevent RSV infections.

"Even in the context of receiving prophylactic treatment, these kids appear to end up hospitalized," Polack said.

With multiple RSV vaccine candidates in the pipeline, it will be important to monitor the response of children with the TLR4 mutation

during vaccine trials, he said.

"This sub-population may or may not respond in the same way as children without the mutation," he said. "They are at risk of failing vaccination and still requiring hospitalization after RSV infection."

Provided by Vanderbilt University Medical Center

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