Scientists solve failed vaccine mystery

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Research led by Johns Hopkins Children's Center scientists has figured out why a respiratory syncytial virus vaccine used in 1966 to inoculate children against the infection instead caused severe respiratory disease and effectively stopped efforts to make a better one. The findings, published online on Dec. 14 in *Nature Medicine*, could restart work on effective killed-virus vaccines not only for RSV but other respiratory viruses, researchers say. The new findings also debunk a popular theory that the 1966 vaccine was ineffective because the formalin used to inactivate the virus disrupted critical antigens, the substances that stimulate the production of protective antibodies.

Instead, researchers said, the problem occurred when the antibodies created by the vaccine failed to successfully bind to the real virus after exposure to it, thereby incapacitating it. Like vaccines against influenza and polio, the 1966 formalin-inactivated RSV vaccine produced antibodies, but these turned out to be defective ones with poor virus-binding ability.

"We have found the root cause of the problem, and in doing so we have uncovered clues that will help us design even safer and more effective vaccines in the future," says senior investigator Fernando Polack, M.D., an infectious disease specialist at Hopkins Children's.

More specifically, in a series of experiments, the research team discovered that the old RSV vaccine failed to trigger a "signaling" mechanism — called toll-like receptor activation — that helps the immune system recognize a virus and mount a defense against it. Toll-

like receptor activation is the first in cascade of immune system responses that occur after infection, firing off signals to other immune cells telling them to produce and release antibodies.

First, the team compared immune system response in three groups of mice: those vaccinated with a placebo, those with a weakened form of the RSV virus, and those with inactivated or killed-virus vaccines. Researchers found that in the last group, the toll-like receptor activation was weak and led to the production of defective antibodies.

Next, they infused the vaccine with a substance that stimulates toll-like receptor activation to see if it would created antibodies better equipped to bind to and neutralize the virus. Indeed, mice vaccinated with the toll-like receptor stimulating form of the inactivated vaccine produced antibodies with better binding and virus-neutralizing ability. Mice immunized with this form of the vaccine had milder symptoms and less inflammation in the bronchi and the lungs when infected with the real RSV.

Source: Johns Hopkins Medical Institutions