Antibody-dependent Enhancement (ADE) and Vaccines

Immune responses to pathogens involve many cells and proteins of the immune system. Early during an infection, these responses are non-specific, meaning that although they are directed at the pathogen, they are not specific to it. This is called innate immunity. Within a few days, adaptive immunity takes over; this immunity is specific to the invading pathogen. Adaptive immune responses include antibodies. A major goal of antibodies is to bind to the pathogen and prevent it from infecting, or entering, a cell. Antibodies that prevent entry into cells are called neutralizing antibodies. Many vaccines work by inducing neutralizing antibodies. However, not all antibody responses are created equal. Sometimes antibodies do not prevent cell entry and, on rare occasions, they may actually *increase* the ability of a virus to enter cells and cause a worsening of disease through a mechanism called antibody-dependent enhancement (ADE).

What is ADE?

ADE occurs when the antibodies generated during an immune response recognize and bind to a pathogen, but they are unable to prevent infection. Instead, these antibodies act as a "Trojan horse," allowing the pathogen to get into cells and exacerbate the immune response.

Is ADE caused by a disease?

CONTACT US
VACCINE EDUCATION CENTER
CONTACT US ONLINE
VEC MAIN MENU
ABOUT THIS SECTION
ARE VACCINES SAFE?
DOSING SAFETY
FEVER AND VACCINES
IMMUNE SYSTEM AND HEALTH
BLOOD-BRAIN BARRIER AND VACCINES
ANTIBODY-DEPENDENT ENHANCEMENT (ADE) AND VACCINES

Most diseases do not cause ADE, but one of the best studied examples of a pathogen that can cause ADE is dengue virus. Dengue virus is one of the most common infections in the world, infecting hundreds of millions and killing tens of thousands of people each year. Unlike viruses like measles or mumps that only have one type, dengue virus has four different forms, called “serotypes.” These serotypes are very similar, but slight differences among them set the stage for ADE. If a person is infected by one serotype of dengue virus, they typically have mild disease and generate a protective immune response, including neutralizing antibodies, against that serotype. But, if that person is infected with a second serotype of dengue virus, the neutralizing antibodies generated from the first infection may bind to the virus and actually increase the virus’s ability to enter cells, resulting in ADE and causing a severe form of the disease, called dengue hemorrhagic fever.

Is ADE caused by vaccines?

On a few occasions ADE has resulted from vaccination:

- Respiratory syncytial virus (RSV) — RSV is a virus that commonly causes pneumonia in children. A vaccine was made by growing RSV, purifying it, and inactivating it with the chemical formaldehyde. In clinical trials, children who were given the vaccine were more likely to develop or die from pneumonia after infection with RSV. As a result of this finding, the vaccine trials stopped, and the vaccine was never submitted for approval or released to the public.

- Measles — An early version of measles vaccine was made by inactivating measles virus using formaldehyde. Children who were vaccinated and later became infected with measles in the community developed high fevers, unusual rash, and an atypical form of pneumonia. Upon seeing these results, the vaccine was withdrawn from use, and those who received this version of the vaccine were recommended to be vaccinated again using the live, weakened measles vaccine, which does not cause ADE and is still in use today.

Both the RSV and measles vaccines that caused ADE were tested in the 1960s. Since then, other vaccines have successfully been created by purifying and chemically inactivating the virus with formaldehyde, such as hepatitis A, rabies, and inactivated polio vaccines. These more recent vaccines do not cause ADE.

A more recent example of ADE following vaccination comes from dengue virus:

- Dengue virus — In 2016, a dengue virus vaccine was designed to protect against all four serotypes of the virus. The hope was that by inducing immune responses to all four serotypes at once, the vaccine could circumvent the issues related to ADE following disease with dengue virus. The vaccine was given to 800,000 children in the

Philippines. Fourteen vaccinated children died after encountering dengue virus in the community. It is hypothesized that the children developed antibody responses that were not capable of neutralizing the natural virus circulating in the community. As such, the vaccine was recommended only for children greater than 9 years of age who had already been exposed to the virus.

Other viral vaccines that target multiple types of a virus have been safely used, including vaccines against polio (3 types), rotavirus (5 types), and human papillomavirus (9 types).

Should I be concerned that my child will develop ADE after receiving a vaccination?

Today's routinely recommended vaccines do not cause ADE. If they did, like those described above, they would be removed from use. Phase III clinical trials are designed to uncover frequent or severe side effects before a vaccine is approved for use. Find out more about how vaccines are developed and approved for use.

Can the new COVID-19 vaccines cause ADE?

Neither COVID-19 disease nor the new COVID-19 vaccines have shown evidence of causing ADE. People infected with SARS-CoV-2, the virus that causes COVID-19, have not been likely to develop ADE upon repeat exposure. This is true of other coronaviruses as well. Likewise, studies of vaccines in the laboratory with animals or in the clinical trials in people have not found evidence of ADE.

References

Dengue

Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med 2018;379(4):327-40.

The risk of developing severe disease from dengue is higher for individuals with a secondary infection than for those with a primary infection. Previous studies indicated that it is possible that CYD-TDV vaccination could mimic a primary infection in patients who had never been exposed to the virus (seronegative), causing their first true exposure to natural infection to result in a severe secondary infection. In efficacy and safety trials of CYD-TDV, excess hospitalizations for dengue were observed among vaccine recipients 2 to 5 years of age, but baseline serostatus was not obtained for all children. Researchers in this study determined the baseline serostatus of the children, aged 2 to 16 years, enrolled in these trials to assess safety and efficacy results based on serostatus. In seronegative children, the likelihood of hospitalization or severe virologically confirmed dengue was much greater in vaccine recipients than those who received placebo. Seropositive vaccine recipients had a

lower likelihood of hospitalization or severe disease compared with placebo recipients.

Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, Deseda C, Chotpitayasunondh T, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015;373:1195-1206.

Investigators assessed the long-term safety and efficacy of a tetravalent dengue vaccine (CYD-TDV) in three clinical trials of more than 30,000 children between the ages of 2 and 16 years of age in Asia and Latin America. Seropositive children had vaccine efficacies of 70% (< 9 years) and 82% (≥ 9 years). Seronegative children had much lower efficacy rates of 14% (< 9 years) and 53% (≥ 9 years). Regarding safety, children vaccinated between 2 to 5 years of age in Asia were shown to have an increased risk of hospitalization secondary to dengue three years after the first vaccine dose compared with children who received placebo. However, the risk of hospitalization in the fourth and fifth years after vaccination was the same as that in children who received placebo. Due to this safety signal in younger patients, CYD-TDV was first submitted for approval for use in children over the age of 9 years. However, after completion of this study, an increased risk of hospitalization and severe disease in children who were seronegative prior to vaccine was found. This caused the manufacturer to change the label to restrict vaccination to subjects who are seropositive at the time of vaccination.

Formalin-inactivated measles vaccine

Martin DB, Weiner LB, Nieburg PI, Blair DC. Atypical measles in adolescents and young adults. Ann Intern Med 1979;90:877-81.

In this case series, the authors describe seven patients aged 12 to 19 years who developed atypical measles 10 to 13 years after receipt of formalin-inactivated measles vaccine (FIMV). Similar to previous reports, atypical measles was characterized by unusual rash, high fevers and pulmonary disease. Additional findings were increased liver enzymes, thrombocytopenia, disseminated intravascular coagulation and possible cardiac involvement.

Fulginiti VA, Eller JJ, Downie AW, Kempe CH. Altered reactivity to measles virus: atypical measles in children previously immunized with inactivated measles virus vaccines. JAMA 1967;202(12):101-6.

Children aged 6 months to 9 years received either three doses of FIMV, or two doses of FIMV followed by one dose of live attenuated vaccine. In this follow-up case series, the authors described 10 children who were hospitalized at the ages of 6 to 8 years with an atypical severe presentation of measles, five to six years after receipt of FIMV. All became abruptly ill with fever (103-105°F) and a rash that appeared within 48 to 72 hours of fever. Most had edema of the extremities, and nine children were diagnosed with pneumonia. All recovered completely. The inactivated measles vaccine was removed from the market in 1967 due to waning

antibody effects and continued reports of atypical measles in vaccine recipients.

Rauh LW and R Schmidt. Measles immunization with killed virus vaccine. Am J Dis Child 1965;109:226-31.
A series of 386 children, aged 6 months to 6 years, were administered three injections of FIMV. Measles antibody titers conferred protection one month after series completion. After one year, 77% of children tested had no detectable antibodies. Booster injections resulted in a rapid rise in virus-specific antibodies, but failed to offer protection the following year. Two-thirds of these children were observed for two to 2 ½ years after receipt of their third dose, during which time a measles epidemic occurred in the community. During that outbreak, 125 previously vaccinated children were exposed to the virus and nearly half developed a measles infection. Atypical forms of measles or severe manifestations were reported in nine children. Atypical measles was characterized by unusual rash, high fevers (e.g., 105°F), and some experienced severe pulmonary complications. This was the first report of atypical measles presentation among those who received an inactivated measles vaccine.

Formalin-inactivated respiratory syncytial virus vaccine (FIRSV)

De Swart RL, Kuiken T, Timmerman HH, van Amerongen G, van den Hoogen BG, et al. Immunization of macaques with formalin-inactivated respiratory syncytial virus (RSV) induces interleukin-13-associated hypersensitivity to subsequent RSV infection. J Virol 2002;76:11561-11569.
Formalin-inactivated whole-RSV preparations adjuvated with alum (FIRSV) were found in previous studies to predispose infants for enhanced disease following subsequent natural RSV infection. The authors in this study reproduced this pathological phenomenon in infant macaques and identified immunological and pathological correlates. Vaccine-induced RSV-specific T cells predominantly produced the Th2 cytokines interleukin (IL)-13 and IL-5. Intratracheal challenge with a macaque-adapted wild type RSV three months after the third vaccination elicited a hypersensitivity response associated with lung eosinophilia. The authors hypothesize that an IL-13-associated asthma-like mechanism resulted in airway hyperreactivity in these animals.

Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 1969;89:405-421.
A formalin inactivated respiratory syncytial virus vaccine (FIRSV) precipitated by alum was administered to infants and children. An outbreak of RSV occurred nine months after the vaccine study was initiated. The authors found that significantly more vaccine recipients under 2 years of age exposed to naturally occurring RSV developed pneumonia compared with those who did not receive the vaccine.

Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol 1969;89(4):449-463.
Two formalin-inactivated viral vaccines — respiratory syncytial virus and parainfluenza — were evaluated in children 4 months to 9 years of age. Both vaccines elicited substantial serum antibody titers in a high proportion of the subjects, but these antibody levels failed to protect against subsequent natural challenge. Infants up to 18 months who received the RSV vaccine and subsequently became infected with RSV tended to have a more severe clinical illness and a much higher rate of eosinophilia than infants who did not receive the RSV vaccine.

Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969;89(4):422-434.
Three vaccines were evaluated in infants between 2 and 7 months of age including formalin-inactivated RSV precipitated in alum, formalin-inactivated parainfluenza type 1, and formalin-inactivated trivalent parainfluenza (types 1, 2 and 3). The RSV vaccine induced virus-specific serum antibodies but failed to protect against natural RSV infection. Worse, 80% of RSV vaccinees required hospitalization at the time of RSV infection whereas only 5% of RSV infections among parainfluenza vaccine recipients resulted in admission to the hospital. Two children died in the RSV vaccine group.

Fulginiti VA, Eller JJ, Sieber OF, Joyner JW, Miniamitani M, et al. Respiratory virus immunization I: A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. Am J Epidemiol 1969;89(4):435-448.
Infants and children aged 6 months to 7 years received either formalin-inactivated trivalent parainfluenza vaccine or formalin-inactivated RSV vaccine. RSV vaccine recipients experienced rises in serum antibodies, but this did not confer protection. Researchers observed an unexpected increased in RSV illnesses requiring hospitalization among RSV vaccinees compared with control groups. This difference was most significant in the 6- to 11-month-old group where 13.7% were hospitalized with RSV illness as compared to only 0.86% of an aged matched unimmunized control group.

SARS-CoV-2 vaccine in nonhuman primates

Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med 2020;383(16):1544-1555.
The induction of CD4 type 2 helper T-cell (Th2) (interleukin-4, -5, or -13) responses has previously been associated with vaccine-associated enhanced respiratory disease (VAERD) in some children who were immunized with inactivated respiratory syncytial virus and measles

vaccines. To determine whether mRNA-1273 (Moderna) vaccine induced Th2 responses, researchers immunized macaques with two doses of either 10 mcg or 100 mcg of mRNA vaccine at four-week intervals and challenged the animals eight weeks later with SARS-CoV-2. Vaccination with mRNA-1273 induced robust SARS-CoV-2 neutralizing activity, rapid protection in the upper and lower airways, and no pathologic changes in the lung. mRNA-1273 induced Th1 and not Th2 cell responses.

Vogel AB, Kanevsky I, Che Y, Swanson KA, Muik A, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. bioRxiv 2020; https://doi.org/10.1101/2020.09.08.280818
Researchers reported the design, preclinical development, immunogenicity and anti-viral protective effect in rhesus macaques of the SARS-CoV-2 modified mRNA vaccine candidate, BNT162b2 (Pfizer BioNTech). Animals were inoculated with two doses of 100ug of mRNA. Seven days after the second dose, a robust Th1 response was observed, but only a minute Th2 response, consistent with the unlikely occurrence of vaccine-associated enhanced respiratory disease, which is associated with Th2 responses.

Gao Q, Bao L, Mao H, Wang L, Xu K, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369(6499):77-81.
Researchers developed a purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc), which induced SARS-CoV-2 specific neutralizing antibodies in mice, rats and nonhuman primates. The vaccine candidate was inactivated using β-propiolactone and mixed with alum adjuvant. Three immunizations using two different doses provided partial or complete protection in macaques. After vaccination, macaques were challenged with SARS-CoV-2 without observable antibody-dependent enhancement of infection or immunopathological exacerbation.

Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science 2020;369:806-811.
Researchers developed a series of six DNA vaccine candidates without adjuvant expressing different forms of the SARS-CoV-2 spike (S) protein and evaluated them in 35 rhesus macaques compared with placebo controls. Vaccinated animals developed humoral and cellular immune responses, including neutralizing antibody titers at levels comparable to those found in convalescent humans and macaques infected with SARS-CoV-2. The DNA vaccines induced Th1 rather than Th2 responses. After vaccination, macaques were challenged with SARS-CoV-2 without observable enhanced clinical disease even with the suboptimal vaccine constructs that failed to protect against infection.

Reviewed by Paul A. Offit, MD, Heather Monk Bodenstab, PharmD on January 05, 2021

NEXT STEPS

CONTACT US

VACCINE EDUCATION CENTER

CONTACT US ONLINE

Materials in this section are updated as new information and vaccines become available. The Vaccine Education Center staff regularly reviews materials for accuracy.

You should not consider the information in this site to be specific, professional medical advice for your personal health or for your family's personal health. You should not use it to replace any relationship with a physician or other qualified healthcare professional. For medical concerns, including decisions about vaccinations, medications and other treatments, you should always consult your physician or, in serious cases, seek immediate assistance from emergency personnel.

3401 Civic Center Blvd.
Philadelphia, PA 19104

Get an Estimate for Services

Understand My Charges

Provide Feedback About My Hospital Visit

Language Assistance Available: English | Español | 繁體中文 | العربية | বাঙালি | Deitsch | اردو | Türkçe | 日本語 | ગુજરાતી | Deutsch | हिंदी | Italiano | Bahasa Indonesia | Tagalog | Polski | Tiế´ng Việt | Français | Português | नेपाली | ਪੰਜਾ | 한국어 | Русский