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Ensuring vaccine safety

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Comprehensive safety testing is based on experience with prior vaccines

There is an urgent need for vaccines to protect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to reduce coronavirus disease 2019 (COVID-19) and stop the current pandemic. Although bureaucratic delays should be reduced to accelerate vaccine availability, there remains the need for extensive safety testing protocols developed by the U.S. Food and Drug Administration (FDA) and other regulatory agencies. COVID-19 vaccines will be safe if regulatory agencies maintain their well-documented safety testing protocols. Safety should be considered at every phase of vaccine discovery, development, and testing. History provides a strong scientific basis for safety evaluation of all vaccine candidates, which must be maintained to realize their enormous potential.

Vaccines are among the most successful medical and public health measures ever implemented (*1*). It is estimated that vaccines prevent ~6 million deaths globally per year (*2*). For example, vaccination eliminated variola virus (which causes smallpox) and nearly all wild poliovirus and has greatly reduced measles virus infection. Vaccines against hepatitis A and B viruses, rubella virus, mumps virus, influenza virus, human papilloma virus, varicella zoster virus (which causes chickenpox in children or shingles in adults), and yellow fever virus are broadly used and highly successful at reducing morbidity and mortality. The historical experience with vaccine development has paved the way for a well-developed path for preclinical and clinical testing of vaccines to ensure their safety and efficacy, leading to safe vaccines that have saved millions of lives.

Empirical experience, including evaluation of vaccine-associated adverse events, indicates the importance of thoroughly assessing safety of vaccine preparations before licensing and widespread use. Lessons learned include that all batches of vaccines must be tested for safety. For example, the need for systematic adherence to formulation standards and safety testing of each batch of formalin-inactivated Salk polio vaccine before deployment became apparent after a tragic incident in 1955. Although nearly all batches of the licensed vaccine were safe, two batches from Cutter Laboratories were contaminated with live poliovirus because of incomplete inactivation. This resulted in abortive polio (characterized by headache, stiff neck, fever, and muscle weakness) in 40,000 individuals, 51 cases of permanent paralysis, and 5 deaths and spread to family and community members (*3*). The Cutter incident led to strict new federal regulations, including current quality control measures to ensure strict adherence to vaccine formulation for inactivation of each vaccine batch. Inactivated polio vaccine preparations have been very safe since (*4*).

An additional level of vaccine safety is provided by understanding the mechanism of action and immune correlates of protection. For some vaccines, correlates of protection, such as the presence of specific neutralizing antibodies, are well established. A clear understanding of correlates of protection can ensure that vaccines induce the optimal immune response for protection while avoiding nonproductive or counterproductive immune responses or disease. Two examples illustrate this point. A formalin-inactivated respiratory syncytial virus (FI-RSV) vaccine developed in the 1960s stimulated moderate amounts of serum antibodies, measured by complement fixation, but failed to protect against RSV infection or disease (*5*). Moreover, most children immunized with this inactivated RSV vaccine and that subsequently became infected with RSV were hospitalized, with enhanced respiratory disease. The FI-RSV vaccine was later found not to induce neutralizing antibodies in vaccinees (*6*) and in a cotton rat infection model. It induced a T helper cell 2 (T_H2)–biased $CD4^+$ T cell response (*7*), which can lead to lack of protective immunity and immune pathology. Lack of viral neutralization and altered T cell responses are believed to have contributed to vaccine-enhanced disease in these immunized individuals.

In another example, the first dengue vaccine, a tetravalent chimeric yellow fever–dengue virus vaccine, reduced incidence of severe dengue disease in older children and was licensed for use in children >9 years of age. However, although overall reduction of severe disease and hospitalization over a 5-year period was observed in the trials, protection was highest in individuals who had been exposed to dengue virus before immunization, whereas immunization increased severe disease in seronegative individuals (*8*, *9*). Protection was lowest against one of the four dengue serotypes (DEN-2),

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suggesting that weak immune responses to DEN-2 or in general in seronegative individuals resulted in antibody-dependent enhancement (ADE) of disease. ADE is caused by nonneutralizing antibodies or antibodies at subneutralizing concentrations that promote infection by enhancing uptake of viral particles into host cells. ADE has been reported to increase infectivity of SARS-coronavirus in certain types of cells in culture (*10*). Given these experiences, current vaccine evaluation in preclinical and clinical studies (see the figure) includes scrutiny of vaccine immunogenicity in relation to correlates of protection to maximize efficacy and minimize potential detrimental effects.

Another lesson learned is that if serious adverse events are detected in a clinical trial, then additional clinical testing is indicated. For example, the first rotavirus vaccine, a rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) with genome segments of human and rhesus rotaviruses, was licensed in the United States in 1998. Rotaviruses cause severe and potentially fatal diarrhea in infants and children. Although the vaccine was effective in preventing gastroenteritis in infants, intussusception (a painful form of bowel obstruction due to bowel prolapse that can be fatal if left untreated) was reported in 5 of 10,054 vaccinees, compared with 1 case in 4633 placebo recipients, a difference that was not statistically significant. The perceived lack of serious adverse effects led to licensure of RRV-TV, with intussusception as a possible rare adverse reaction. However, after its approval and in the first year of vaccine use, 15 cases of intussusception were reported in vaccinees, in contrast to only four cases in the 7 years preceding vaccination, triggering suspension of the vaccine in 1999 (*11*). This example illustrates the importance of careful evaluation of any adverse reaction and postlicensure surveillance to ensure vaccine safety. Large prelicensure trials of two later rotavirus vaccines, a pentavalent human-bovine viral reassortant vaccine (RV5) and a monovalent single-strain human rotavirus vaccine (RV1) with compositions different from that of RRV-TV, demonstrated very low incidence of intussusception, and these vaccines are now widely approved for use.

In 1976, an outbreak of influenza that resulted in one death among Army recruits at Fort Dix, New Jersey, followed by spread through the base, was ascribed to influenza virus isolates similar to the 1918 pandemic H1N1 virus that killed millions of people. Fearful that a potentially pandemic influenza virus was emerging, an emergency vaccine initiative was approved by President Ford and funded by Congress. Meanwhile, scientific questions arose, including genetic evidence that the New Jersey isolates were similar to swine (H1N1) influenza viruses circulating in the United States at the time (*12*) and doubts about the virulence of the virus isolates, both suggesting that this was not an emerging pandemic virus. In addition, there was evidence that the vaccine being produced lacked an antigenic form of the viral neuraminidase protein, which could render it less efficacious. President Ford nevertheless implemented the vaccine initiative.

The influenza vaccine was tested in ~7000 individuals in the spring of 1976 and was deemed to be safe, with broad immunization starting on 1 October. About 25% of the U.S. population was immunized before ~450 cases of the paralytic Guillain-Barré syndrome (GBS) disease emerged, a statistically significant increase above the normal population incidence (*13*). This influenza immunization program was terminated in December 1976 with severe consequences, including diminished public confidence in vaccines and the public health care system. Later studies have shown minimal GBS associated with other influenza virus vaccines (*13*); thus, this particular vaccine formulation was likely problematic. Potential lack of neuraminidase activity, contamination with other microbes, and induction of autoimmune antibodies have all been suggested to account for these adverse effects.

As a result of the observations from the RRV-TV and 1976 swine flu vaccines, current regulatory practices require monitoring of rare adverse events pre- and postlicensure with detection of serious adverse events triggering a pause to trial or use. Such a safety pause enables study of adverse events to assess whether the vaccine trial or use can be resumed as deemed appropriate. Indeed, such safety pauses have occurred in current COVID-19 vaccine trials, underscoring the value of extensive regulatory safety protocols, which should not be rushed or undermined.

History has also taught us the importance of continued surveillance of potential vaccine-related adverse events and measurement of immunogenicity and outcomes even after licensure. Such surveillance—for example, through the U.S. Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS) and the FDA Biologics Effectiveness and Safety (BEST) electronic medical record–based platform—can confirm safety and increase understanding of the immune correlates of protection and mechanisms of immunogenicity to further enhance vaccine development.

Multiple COVID-19 vaccine trials are currently being conducted in parallel, with many additional candidates in preclinical development. A decision regarding one of these clinical trials that enables vaccine use before full regulatory approval—for example, through emergency use authorization (EUA)—would accelerate deployment at the potential risk of undermining the ability to recruit additional participants for that and other trials, thereby impairing collection of normally comprehensive data regarding safety, immunogenicity, efficacy, and durability of protection (*14*). To enhance public confidence in vaccines by providing transparency, the FDA Center for Biologics Evaluation and Research (CBER) has published master protocols for SARS-CoV-2 vaccine safety and effectiveness evaluation (*15*). Overall, the interests of

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vaccinees, vaccine developers, pharmaceutical companies, and regulatory agencies are aligned on the importance of ensuring vaccine safety.

There is an urgent need for COVID-19 vaccines and exciting progress to that end, but there remains a critical public health obligation to conduct rigorous evaluation to ensure safety as well as efficacy. Vaccines remain one of the most successful biomedical tools for prevention of disease. The urgent need for COVID-19 vaccines must be balanced with the imperative of ensuring safety and public confidence in vaccines by following the established clinical safety testing protocols throughout vaccine development, including both pre- and postdeployment.

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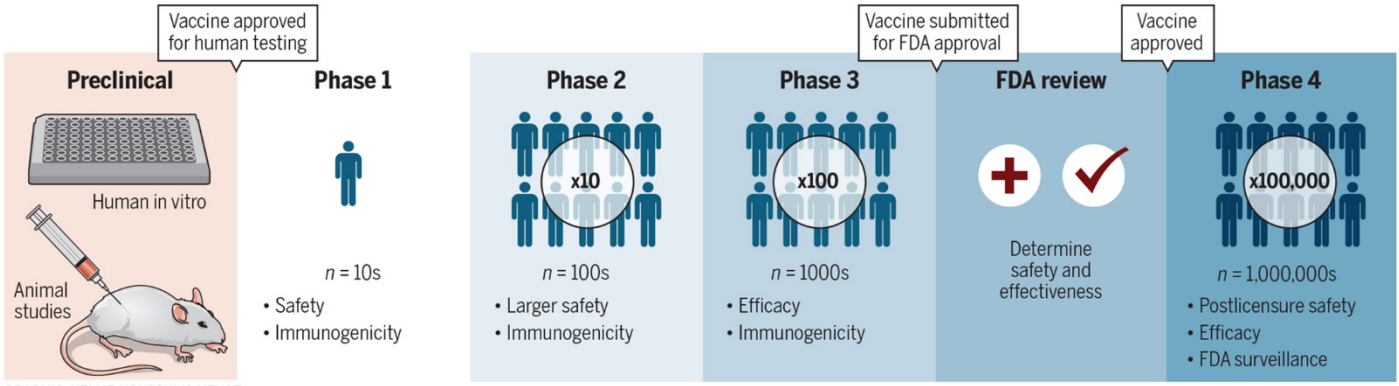
Vaccine safety evaluation

Safety is considered at every phase of vaccine discovery and development. Upon licensure, vaccines enter phase 4, whereby surveillance approaches by regulators, such as the U.S. Food and Drug Administration (FDA), monitor potential vaccine side effects.



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