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Viral Vaccines

MR Schleiss, Division of Infectious Diseases, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN, United States

Glossary

Adjuvant An exogenous immunostimulatory agent added to vaccines to enhance immunogenicity. Adjuvants improve immune response and stimulate humoral and/or cellular immunity to improve the protective capacity of vaccines.

Attenuation The process of modification of the biology of a strain of virus by serial passage in tissue culture. Attenuation in cell culture has been a hallmark of vaccine discovery and has provided the basis by which many vaccines currently in clinical practice were developed.

Contact immunity A phenomenon whereby individuals acquire vaccine-induced immunity by virtue of close contact with immunized individuals who transmit the live, attenuated strain of vaccine to the naïve individual. Contact immunity can, in effect, immunize unvaccinated individuals secondarily through contact with vaccinated individuals. This is known to be an attribute of oral polio vaccination.

DNA vaccine Vaccine strategy in which a recombinant DNA molecule encoding a viral gene product (protein) of interest is administered to an individual, toward the goal of inducing a protective immune response.

Herd immunity Vaccine-induced protection of a population based on the acquired immunity of a large percentage of individuals residing in that community. When vaccine rates are high, the likelihood of herd immunity is high, and disease rates are low because of the lack of susceptible individuals.

Intussusception A form of intestinal blockage, usually observed in infants, where a portion of bowel collapses into the lumen of the adjacent bowel, creating a 'telescope'-like effect. This phenomenon was observed with first-generation rotavirus vaccines; though never causally proven, it did lead to the withdrawal of one rotavirus vaccine from the market.

mRNA vaccine A novel vaccine strategy, first evaluated in human subjects in the context of the COVID-19 pandemic, in which a messenger RNA (mRNA) encoding a viral gene product (protein) of interest is administered to an individual, toward the goal of inducing a protective immune response.

Subunit vaccine A vaccine designed and manufactured to induce antibody responses against one or more particular proteins or constituents of a pathogenic virus. Subunit vaccines typically utilize cloning technologies to express immunological targets of interest in a variety of expression systems.

VAPP Vaccine-associated paralytic poliomyelitis. This occurs when the specific attenuating mutations in the oral polio vaccine are lost due to reversion to wild-type sequence. The resulting revertant virus is capable of neurovirulence leading to paralytic polio.

Vectored vaccine A vaccine approach in which an immunogen of interest (such as SARS-CoV-2 Spike protein) is inserted into another, attenuated viral vector. Immunization of the individual with the vector in turn induces an immune response to the gene product of the pathogen, resulting in protective immunity against that virus.

Introduction

Credit for the first use of vaccines in humans has historically gone to Edward Jenner, who is considered the pioneer of the smallpox vaccine (Eyler, 2003). The work of Jenner took place in the late eighteenth century, but in fact, the history of smallpox vaccination dates back to much earlier times in human history, when the process of "variolation" (inoculating a susceptible individual with the dried scab or secretions from another person with the smallpox) was practiced as long ago as the tenth century in China (Gross and Sepkowitz, 1998). Smallpox vaccination represents the prototype of a "live, attenuated" viral vaccine, discussed in the following section (see also Table 1). The second category of vaccines in clinical use is the so-called "subunit" vaccine, typically based on the immunization of a susceptible individual with one or more proteins important in immunity against the pathogen of concern (Table 2). Usually these protein-based vaccines are administered with an immunostimulatory adjuvant (defined below). Broadly speaking, nucleic acid-based vaccines (DNA and mRNA) can be considered as "subunit" vaccines, since they are typically predicated on the administration of a nucleic acid sequence encoding a single (or limited number of) viral gene product(s). Finally, there is a sub-category of subunit vaccines in clinical use referred to as "vectored" vaccines. These vaccines use an innocuous and attenuated agent, usually a replication-incompetent virus, to express a foreign gene from a heterologous pathogen. Expression of the gene product following immunization induces protective immunity to the pathogenic virus. Most of the important vaccines used in clinical practice today fall into one of these categories. In this article, clinically important viral vaccines are listed in the accompanying tables, and some of the most important viral vaccines used in medical practice today are reviewed and compared in the text. The impetus behind the rationale for a vaccine's design is provided, as well as the proposed mechanism(s) of protection. The need for new, novel immunizations against viral pathogens for which no vaccines are currently available is briefly discussed.

Table 1   Live, attenuated viral vaccines in clinical practice.

Vaccine	Indication	Route of administration	Comments
Smallpox (vaccinia)	Smallpox prevention.	Intradermal.	• Not current recommended for routine use. • Potential future role in bioterrorism disease control?
Oral polio vaccine (OPV)	Polio prevention.	Oral; three-dose series.	• Serotypes 1–3. • Contact immunity. • Intestinal/mucosal immunity. • Risk of VAPP. • No longer used in developed world.
Live, attenuated influenza vaccine (LAIV)	Influenza prevention.	Intranasal.	• Attenuated by cell culture passage at 25 °C. • Induces mucosal (IgA) responses in addition to IgG response. • Approved for ages 2–49 years
Mumps, measles, and rubella vaccine (MMR)	Prevention of mumps, measles and rubella infections.	Subcutaneous (preferred) or intramuscular.	• Three vaccines are combined for convenience and ease of dosing. • Vaccine initiated at 15 months. • Second dose required in later childhood.
Rotavirus vaccine	Prevention of rotavirus infection (epidemic gastroenteritis).	Oral; two- or three-dose series.	• Two vaccines currently licensed in U.S. are either human rotavirus-derived attenuated vaccine or bovine/human reassortants. • Vaccination begins in the first 1–2 months of life. • Intestinal/mucosal immunity. • Serum IgG response.
Live, attenuated varicella-zoster virus (VZV) vaccine for chicken pox (varicella); live, attenuated vaccine for Herpes Zoster (shingles)	Prevention of chicken pox; prevention of shingles (Herpes Zoster).	Subcutaneous or intramuscular.	• Protects against chicken pox when administered in two-dose series to VZV seronegatives. • Protects against reactivation (shingles or herpes zoster) when given to adults with past history of chicken pox. • Live attenuated Zoster vaccine no longer available in the U.S. but still in use in other countries.
CYD-TDV	Prevention of Dengue fever.	Subcutaneous administration; three-dose series.	• Live attenuated tetravalent chimeric vaccine. • Three-doses at every 2 month intervals. • CYD-TDV is partially effective in preventing infection, but vaccination may lead to severe disease in those who have not been previously infected and then acquire natural infection.

Table 2 Killed/inactivated/subunit/vectored viral vaccines used in clinical practice.

Vaccine	Indication	Route of administration	Comments
Hepatitis A	Prevention of hepatitis A infection.	Intramuscular; two-dose series.	• Formalin-inactivated virus proteins from cell culture. • Adjuvanted with aluminum hydroxide. • Induces protective IgG response. • Recommendation for universal childhood immunization.
Hepatitis B	Prevention of hepatitis B infection.	Intramuscular; three-dose series. A combined hepatitis A/hepatitis B vaccine, 'Twinrix,' is also licensed in the U.S. (see text for details).	• Based on single viral protein, hepatitis B surface antigen (HBsAg). • Expressed using cloned, recombinant expression in *Saccharomyces cerevisiae.* • Adjuvanted with aluminum hydroxide. • Induces protective IgG response to HBsAg. • Recent new two-dose recombinant HB surface antigen vaccine approved, similar to previous vaccines, includes a novel CpG 1018 adjuvant, a 22-mer phosphorothioate-linked oligodeoxynucleotide. • Cancer prevention vaccine. • Universal recommendation for childhood immunization.
Inactivated/ subunit influenza vaccines	Influenza prevention.	Intramuscular.	• Formalin-inactivated ('split virion') vaccines. • Both trivalent and tetra-valent formulations available. • Mechanism of action: induction of anti-HA (hemagglutin) and influenza virus-neutralizing IgG responses. • Vaccine virus cultivated in embryonated eggs; other cell culture systems are available including eucaryotic cell culture and insect cell culture for egg-allergic patients. • A high-dose vaccine with 4 times the total influenza protein in licensed in the US for individuals >65 years. • An adjuvated flu vaccine with MF59C.1 adjuvant is licensed for individuals >65 years. • Universal immunization against influenza recommended for all individuals >6 month of age in US.
HPV vaccine	Prevention of HPV infection.	Intramuscular; CDC recommends that 11- to 12-year-olds receive two doses of HPV vaccine 6 to 12 months apart; only two doses are recommended if vaccination started at age 9 and through age 14, but teens and young adults who start the series later, at ages 15 through 26 years, need three doses of HPV vaccine.	• Bivalent (16, 18). Quadrivalent (6, 11, 16, 18) and nine-valent (9vHPV; types 6, 11, 16, 18, 31, 33, 45, 52, and 58) have been licensed by FDA. • Vaccine manufactured as recombinant protein in a yeast cell culture system (*Saccharomyces cerevisiae*). • Nine-valent formulation is the only HPV vaccine currently distributed in the U.S.
Japanese Encephalitis Virus Vaccine	Prevention of Japanese Encephalitis Virus infection.	Two-dose series, subcutaneous administration.	• Mosquito-borne *Flavivirus* infection. • Endemic in Western Pacific and Southeast Asian Regions. • Formalin-inactivated, multi-component viral vaccine currently is approved in the USA, but DNA vaccines and attenuated vaccines also in various stages of clinical development globally.
Herpes Zoster (Shingles) vaccine	Prevention of Herpes Zoster.	Intramuscular, two-dose series.	• Based on VZV glycoprotein E protein. • Adjuvanted with AS01B adjuvant. • Protects against reactivation (shingles or Herpes Zoster) when given to adults with past history of chicken pox.
SARS-CoV-2 (COVID 19) vaccines	Prevention of infection and/or reduction of disease, reduced risk of hospitalization and death due to COVID-19.	mRNA/lipid nanoparticle vaccines (BNT162b2 and mRNA-1273): intramuscular administration, 2 dose series plus a third (booster) dose. Adenovirus-vectored vaccine (Ad26.COV2·S COVID-19 vaccine): initial dose by intramuscular route followed by booster dose.	• BNT162b vaccine requires two doses given 21 days apart. • The mRNA1273 vaccine requires two shots spaced 28 days apart. • Recommendation for third (booster) dose for both mRNA vaccines 6 months following second dose. • Both mRNA vaccines encode for the SARS-CoV-2 (COVID) "Spike" glycoprotein (but expressed as RNA molecule). • Ad26.COV2·S COVID-19 vaccine administered at least 2 months following initial dose. • Ad26.COV2·S COVID-19 vaccine expresses Spike protein in the context of recombinant adenovirus vector (and hence has a replication incompetent virus vector backbone), and does not contain adjuvant.

Live, attenuated viral vaccines

Smallpox vaccine

As noted, the first known vaccine used in the history of humanity was a vaccine against smallpox (also known as variola). Edward Jenner received credit for developing the first smallpox vaccine. As history has it, Jenner observed that milkmaids exposed to cowpox appeared to be "resitant" to acquisition of smallpox. Jenner tested whether inoculation of subjects with material from cowpox lesions protected individuals against smallpox upon direct exposure. Indeed, the approach was successful, and the term "vaccination" (derived from the Latin word *vacca*, meaning "cow") was used to describe the procedure. Although Jenner receives credit for developing the smallpox vaccine – and, indeed, creating the field of vaccinology – other contemporaries of Jenner had observed the protective effect against smallpox conferred by exposure to cowpox, most notably Dr. Benjamin Jesty (Eyler, 2003), in the years leading up to Jenner's groundbreaking experiments.

Although initial approaches to smallpox vaccination utilized cowpox virus, the smallpox vaccine historically employed in clinical practice was based on vaccinia, another related poxvirus, but one that has minimal potential for virulence in healthy, immune-competent humans. Smallpox vaccine administration was unique compared to most other viral vaccines, insofar as it was administered by skin prick using a novel, two-pronged needle. Smallpox vaccine was extraordinarily successful globally and, indeed, smallpox is today the only disease in the history of humanity eradicated by immunization (Smith, 2013). Globally, the last known case of smallpox was reported in Somalia in 1977, and routine smallpox vaccination was discontinued in the United States in the early 1970s. After the terrorist attacks of September 11, 2001, smallpox immunization was reinitiated in some potentially high-risk populations, including health care providers and military personnel, in anticipation of the possible use (never realized) of weaponized smallpox virus by terrorists as a biological weapon (Arita, 2005). Since smallpox vaccine was discontinued, there has been an apparent emergence of the highly related monkeypox infection in humans, due to the loss of cross-protective immunity formerly conferred by smallpox immunization (Sklenovská and Van Ranst, 2018).

To this day, the principles of Jenner's approach – based on the recognition of strong biological similarities of infectious syndromes across different species – are employed in the design and production of live, attenuated viral vaccines for human use. This is sometimes referred to as a "Jennerian" approach, and can include propagation of human pathogens on cells of heterologous species toward the goal of attenuation of the pathogens (varicella vaccine, measles vaccine), or actually using components of the related vertebrate virus (rotavirus vaccine) in creating the human vaccine. Individual examples are considered in further detail below.

Live, attenuated polio vaccine

Poliovirus is a member of the enterovirus family of human pathogens. Although most individuals with polio infection have a mild, self-limited illness, a small but substantial percentage will have polio infection spread to the brain and/or spinal cord, where it can lead to paralysis and potentially death. By the early 1950s in the United States, polio epidemics had become devastating. For example, between 1951 and 1954, there were over 10,000 cases of paralytic poliomyelitis reported every year to the Centers for Disease Control and Prevention (Nathanson and Kew, 2010).

Two polio vaccines emerged in clinical practice in the late 1950s/early 1960s (Melnick, 1996). The first vaccine, the so-called Salk vaccine, is a killed, whole-virion protein vaccine (reviewed below). The second licensed vaccine, the Sabin vaccine, is a live, attenuated vaccine. Both vaccines are still used today, although the Sabin vaccine is not currently used in the United States. The Sabin vaccine is made up of three different serotypes of poliovirus (types 1–3), all of which can cause paralytic polio. The vaccine was originally created by passage of polio in primary monkey and human diploid cell cultures, at subphysiological temperatures that allowed growth of virus, but facilitated the accumulation of attenuating mutations. Following tissue culture passage, mutations accumulate in the sequence of all three strains that lead to a loss of virulence and an inability of the viruses to produce paralysis. These mutations have been mapped in detail (Kew et al., 2005). One of the features of these attenuating mutations is a reduction in the ability of viral messenger RNA to be translated by the ribosome.

The oral polio vaccine (OPV) is administered in a four-dose series. The vaccine contains mixtures of all three attenuated polioviruses. The attenuated vaccine strains replicate very efficiently in the gastrointestinal tract, as does wild-type poliovirus, which probably contributes to an enhanced immune response compared to inactivated polio vaccine. This so-called intestinal immunity appears to include mucosal IgA responses that enhance the protective effect of the vaccine. Moreover, the vaccine virus is excreted in the stool of immunized patients. This excreted vaccine virus can, in turn, be ingested by a nonvaccinated individual, leading to secondary (contact) immunization, via the fecal–oral route of ingestion. Thus, this creates the potential for "contact immunity", namely, the idea that others will be secondarily immunized by being in close contact with individuals who receive the vaccine. This phenomenon contributes to the preference for oral polio vaccination in regions where wild-type polio is still highly endemic. Unfortunately, polio vaccine virus also has the potential to revert back to wild-type sequence in the gastrointestinal tract in immunized patients, and can in fact revert to a fully neurovirulent genotype, particularly in children with immune deficiency. This exposure to revertant virus can lead to paralysis, and this "vaccine associated paralytic poliomyelitis" (VAPP) phenomenon was responsible for 8–10 cases of polio in the United States every year until OPV use was discontinued in the United States in the late 1990s. Wild-type poliovirus has been absent from the Western hemisphere since 1991, although occasionally neurovirulent revertant strains of polio are still observed (Alexander et al., 2009), presumably due to importation from countries still using

OPV. Some of these revertant strains are capable of circulating in vaccine-naïve populations and producing paralytic poliomyelitis (Gumede et al., 2013). For regions of the world where polio is still endemic and epidemic, however, OPV has been considered to be the preferred vaccine for population-based immunization. Considerable progress has been made toward global polio eradication (Modlin et al., 2021), facilitated by the global SARS-CoV-2 pandemic, since the recent global vaccination drive against COVID-19 has increased the public dialog about the great need for vaccines, including polio vaccine (Ali et al., 2021).

Influenza vaccine (live, attenuated)

Influenza is an RNA virus in the *Orthomyxoviridae* family. There are two major subtypes of influenza virus: influenza A and influenza B. Both are important human pathogens, although humans are not the natural host for influenza (wild aquatic birds are the natural host). Influenza has a segmented RNA genome and influenza A virus can undergo extensive recombination in nature, leading to the appearance of genetically variant strains not previously encountered in the human population. When this process – known as "antigenic shift" – occurs, an influenza pandemic can ensue, leading to extensive mortality. The influenza pandemic of 1918 resulted in an estimated 50,000,000–100,000,000 deaths globally (Morens and Fauci, 2007). Even in a "normal" influenza season, it is estimated that 40,000–50,000 deaths every year in the United States are attributable to influenza infection. Universal annual influenza administration is recommended for everyone over 6 months of age in the United States.

Live, attenuated influenza vaccines (LAIVs) have only recently become available for clinical use. These vaccines are prepared by passaging clinical isolates of influenza in cell culture using subphysiological temperatures. This process of "cold adaptation" – used in the generation of other live, attenuated viral vaccines considered in this article – led to the development of the current LAIVs used in clinical practice (Jang and Seong, 2012). Since the process of cold adaptation in cell culture was undertaken at temperatures (25 °C) incompatible with replication of virus at core body temperature (37 °C), these vaccines are highly attenuated and extremely safe. The vaccine is administered in the form of a nasal drop or spray on an annual basis. The vaccine is trivalent, containing two strains of influenza A and a single strain of influenza B, or tetravalent, containing two strains of influenza A and two strains of influenza B, depending upon the manufacturer. The strains chosen to compose the vaccine each flu season depend upon what strains of influenza have recently circulated, or are predicted by public health officials, to be circulating in the upcoming influenza "season". LAIV is not recommended for children under 2 years of age, or individuals over 50 years. The mechanism of protection is the induction of IgG antibody to influenza, in particular hemagglutination-inhibition antibody.

Measles vaccine

Measles is a highly contagious viral infection spread from person to person predominately by aerosol (droplet) route. It is a member of the *Parymyxoviridae* family of viruses. Measles infections used to be so ubiquitous in nature that it is assumed that all individuals born in the United States before 1957 are immune to the measles virus. Prior to the advent of vaccination, measles (also known as rubeola) caused considerable mortality globally, with over 2 million deaths annually in children (Cutts et al., 2013). Measles infection causes cough, coryza (runny nose), and conjunctivitis, as well as a classic morbilliform ("measles-like") rash. In addition to the classic rash of rubeola, measles infection is responsible for severe, occasionally fatal pneumonia, tracheobronchitis, and encephalitis. Measles infection can also produce long-term complications, in particular subacute sclerosing panencephalitis, a chronic and uniformly fatal encephalitis caused by persistence of measles virus in the central nervous system. Measles infection strongly suppresses the host immune system and predisposes patients (particularly young children) to develop other serious infections, including tuberculosis. Remarkably, measles infection has been shown to "erase" immune memory, potentially resulting in the loss of protection conferred by other vaccines (Petrova et al., 2019). Measles is also an important cause of blindness in the developing world. Although considerable progress has been made in preventing measles-associated morbidity and mortality, over 100,000 measles deaths occurred in 2010, underscoring the need for continued vigilance in vaccination programs (Cutts et al., 2012).

Measles vaccine is a live, attenuated vaccine. Attenuation of this virus occurred following serial passage in a nonpermissive cell line, in the case of measles, cells of avian origin. There have been several measles virus variants used as vaccines in clinical practice since the advent of immunization programs in the early 1960s. The original vaccine strain was named the "Edmonston" strain, after the child from whom the wild-type virus was originally isolated (Hilleman, 1992). The process by which serial passage of the measles virus in cell culture produces attenuation remains unclear, although a recent study demonstrated varying amino acid substitutions in all of the viral proteins encoded by the measles genome in vaccine strains (Bankamp et al., 2011). Measles vaccine is administered by the subcutaneous route, typically at 15 months of age. This vaccine is usually combined with the mumps and rubella vaccines (hence, the MMR vaccine, for mumps–measles–rubella). A second dose of vaccine is recommended later in childhood. The vaccine appears to work by induction of antibody responses to measles envelope glycoproteins, particularly the hemagglutinin protein involved in binding of measles virus to its cellular receptor (Hashiguchi et al., 2011).

Mumps vaccine

Mumps is a paramyxovirus and, as such, highly genetically related to other common childhood infections such as measles, respiratory syncytial virus, and parainfluenza virus. Mumps infections can be associated with parotitis, orchitis (rarely causing infertility), aseptic meningitis, and sensorineural deafness.

Mumps vaccine is based upon attenuating serial passage of what was originally a clinical isolate of mumps virus, the "Jeryl Lynn" strain. This strain is actually a mixture of two distinct, closely related strains (Afzal et al., 1993). Other attenuated strains, including the Zagreb strain, have been used in the development of live attenuated mumps vaccine (Ivancic et al., 2005). The precise molecular basis of attenuation is not known. The vaccine is administered by subcutaneous or intramuscular route, typically in combination with measles and rubella vaccine (MMR vaccine). The protective mechanism appears to be via induction of antibody to mumps virus surface glycoproteins. Mumps outbreaks have occurred on a university campus in spite of the fact that 95% of the affected students had received two doses of the MMR vaccine. The susceptibility appeared to be related to a suboptimal mumps antibody titer (Cortese et al., 2011), suggesting that future modifications of mumps vaccine will be required.

Rubella vaccine

Rubella virus is an enveloped, single-stranded, positive-sense RNA virus belonging to the *Togaviridae* family. Although togaviruses are typically vector-borne infections, rubella is the notable exception, being transmitted instead by a respiratory droplet route. Humans are the only known natural host for rubella virus. Rubella infection, commonly known as the "German measles", usually results in a mild illness with an accompanying exanthem in adults and children; however, rubella produces serious consequences in the pregnant patient, where fetal infection can lead to severe anomalies including microcephaly, sensorineural deafness, and cardiac defects (Freij et al., 1988). An ophthalmologist, Norman Gregg, offered the first description of congenital rubella syndrome (CRS) in 1941, while investigating an epidemic of neonatal cataracts (Gregg, 1947). Not until the global pandemic of 1964–65, however, were the multiple teratogenic manifestations of CRS fully appreciated and the permanent neurodevelopmental consequences for newborns completely recognized. The capacity to grow the virus in tissue culture led rapidly to the development of the vaccine and to a reduction in CRS in the United States and other developed countries.

Rubella vaccines are classic live attenuated viral vaccines, prepared through the process of long-term cell culture passage, which in turn leads to attenuating mutations in wild-type sequences. In clinical practice, most vaccines are derived from the Wistar RA 27/3 strain of virus. Although the strains used in vaccines have been sequenced, the molecular basis of attenuation is unclear (Kakizawa et al., 2001). The vaccine is administered by subcutaneous route or intramuscular route, typically in combination with measles and mumps vaccine (MMR vaccine). The protective mechanism appears to be via induction of antibody to rubella virus surface glycoproteins. Rubella has been eradicated from the Western Hemisphere (Plotkin, 2021), although routine MMR administration continues to be recommended to guard against any resurgence of disease. A combination vaccine containing both MMR and Varicella vaccine – 'MMRV' vaccine – has been licensed in the United States. Unless the parent expresses a preference for MMRV vaccine, the CDC recommends that MMR vaccine and varicella vaccine should be administered as separate injections for the first dose in children 12–47 months of age, with use of MMRV combination vaccine reserved for use as a "booster" dose in later childhood.

Rotavirus vaccine

Rotaviruses are members of the *Reoviridae* family. They are unique among pathogenic viruses by virtue of the fact that their genomes are double-stranded, segmented, RNA genomes. Rotavirus, prior to the advent of vaccination, was the most important cause of viral gastroenteritis, particularly in children (Vesikari, 2012). Rotavirus infection in young children can be responsible for severe diarrhea and attendant fluid and electrolyte abnormalities, and causes considerable mortality in the developing world, where supportive care resources are limited. It was estimated that, globally, rotavirus infection caused more than 450,000 deaths in children under 5 years of age in 2008 (Tate et al., 2012).

Rotaviruses are common in vertebrates, and such viruses (i.e., rhesus macaque rotavirus, bovine rotavirus) share many molecular and biological similarities with human rotavirus. These similarities have been exploited in vaccine design. The first human rotavirus vaccine (licensed in the late 1990s) was a so-called "rhesus reassortant" virus made up of four live viruses: a rhesus rotavirus (serotype G3) and three rhesus–human reassortant viruses (comprising both human and rhesus rotavirus components) that were specific for serotypes G1, G2, and G4. Thus, the vaccine was designed to protect against the four rotavirus serotypes that were responsible for most rotavirus disease in the United States at that time (Vesikari, 2012). This vaccine was successful in preventing rotavirus disease in children following a three-dose series, but was withdrawn from the market because of a possible association with a complication known as intussusception, a complication resulting in intestinal blockage (Peter and Myers, 2002). Subsequently, two new rotavirus vaccines were licensed in the United States and remain in widespread use. These newer vaccines do not appear to carry a risk of intussusception. The first is a live, attenuated human rotavirus vaccine derived from an infant with rotavirus gastroenteritis (G1 strain). This vaccine protects across most of the different serogroups of rotavirus in circulation, not just the G1 serotype. It is recommended for use in a two-dose schedule beginning at 6 weeks of age. The second is another human–animal (bovine) reassortant vaccine. This vaccine contains five live reassortant rotaviruses: four of these express the G1, G2, G3, or G4 VP7 protein from their respective parent human strain and an attachment protein from a bovine strain, and the fifth expresses an attachment protein from a human strain and a VP7 protein from a G6 bovine strain (Dennehy, 2008). This vaccine is recommended for use in a three-dose series, at 2-month intervals, beginning at 6–12 weeks of age. Both vaccines are highly effective in preventing rotavirus infection.

All licensed rotavirus vaccines are administered by the oral route, analogous to the use of the OPV. The correlate of protective immunity induced by vaccination appears to be IgG antibody. However, there is some evidence that an equally important correlate of protective immunity following vaccination may be the IgA response (Patel et al., 2013).

Varicella-zoster virus vaccine

Varicella-zoster virus (VZV) is the etiologic agent of chicken pox. Although most children with chicken pox have an uneventful recovery, prior to the advent of vaccination there were approximately 100 varicella deaths in otherwise immune-competent children in the United States every year, due to pneumonia, neurological complications such as encephalitis, or secondary infections caused by *Streptococcus pyogenes* (Nguyen et al., 2005). As a member of the *Herpesviridae* family of viruses, it is capable of establishing latent infection in the dorsal root ganglia, where it resides in quiescent form for years or even decades before reactivating. When VZV reactivates, it produces a rash on the skin surface corresponding to the region of the skin innervated by that particular ganglia; such a reactivation is known as Herpes Zoster or "shingles" (Schleiss, 2009). Herpes Zoster can lead to postherpetic neuralgia, which can cause debilitating pain for prolonged periods of time, particularly in elderly patients (Gershon and Gershon, 2013). Hence, there is a strong medical rationale for a VZV vaccine both to prevent chicken pox (vaccine given to VZV-naïve subjects) as well as prevent episodes of zoster (vaccine given to those with a history of chicken pox).

VZV vaccine was derived from a clinical isolate known as the "Oka" strain. This strain was originally obtained in the early 1970s from a young child with chicken pox (Takahashi et al., 1974), and was passaged in cell culture, including extensive passages in both guinea pig cell culture as well as human cells (Takahashi et al., 2008). Some of the cell culture passages were at a reduced temperature (34 °C). As is the case for so many other live, attenuated viral vaccines, the precise molecular basis for the attenuation of the virus was unknown at the time of the vaccine's licensure, although recent studies have begun to shed light on the specific molecular mutations that arose during serial tissue culture passage that appear to have contributed to the reduction of virulence (Peters et al., 2012). The vaccine has been variably used in the United States in three formulations: a monovalent formulation ("Varivax") for children and young adults; MMRV vaccine; and a monovalent formulation for adults over 60 years of age for prevention of herpes zoster (shingles). The vaccine is given subcutaneously. Two doses of vaccine are administered for prevention of chicken pox, while a single dose of vaccine had been recommended for older individuals receiving the vaccine to prevent shingles. Although the live, attenuated shingles vaccine is still available in some countries, it is no longer available in the United States, and has largely been supplanted by the adjuvanted, VZV glycoprotein E subunit vaccine, which has been shown to be highly effective at preventing shingles (Heineman et al., 2019).

Subunit viral vaccines

Hepatitis A vaccine

Hepatitis A is an RNA virus in the *Picornaviridae* family. It is readily transmissible by the fecal–oral route and is highly contagious. Food-borne outbreaks are common. Infection leads to liver inflammation ("hepatitis"), vomiting, diarrhea, and jaundice. Jaundice may be absent in young children with acute infection. Although most infections are self-resolving, infection can lead to fulminant hepatic failure in some cases (Brundage and Fitzpatrick, 2006). Subunit vaccines based on formalin-inactivated hepatitis A virus, cultivated in MRC-5 cells, are licensed and marketed by two manufacturers in the United States. Hepatitis A vaccine is also combined with hepatitis B in another vaccine licensed in the United States, a product known as "Twinrix". Both are adjuvanted with aluminum hydroxide adjuvant. Two doses, given by intramuscular route and separated by at least 6 months, are recommended. The mechanism of protection is believed to be by induction of hepatitis A-specific IgG antibody response.

Hepatitis B vaccine

Hepatitis B virus is a double-stranded DNA virus that is a member of the *Hepadnaviridae* family. It is a highly contagious virus, spread by exposure to infectious blood and body fluids. Infection leads to liver inflammation ("hepatitis"), vomiting, jaundice, and occasionally death. It is common for infected individuals to become carriers of hepatitis B, meaning that infection remains active. Hepatitis B is associated with cirrhosis of the liver and hepatocellular carcinoma. It is estimated that one-third of the world's population has been infected with hepatitis B, and that over 350 million people are chronic carriers (Chen, 2010). Given the causal associations between hepatitis B and mortality, development of an antiviral vaccine was a major public health priority.

The first vaccine licensed for human use for hepatitis B was a purified plasma preparation from patients with active hepatitis B infection. These individuals had high concentrations of hepatitis B proteins in serum, and purification of these proteins (including formalin inactivation) allowed their use as a vaccine. This vaccine was licensed in the early 1980s and administered by intramuscular route in a three-dose series (Szmuness et al., 1981). Although this vaccine was safe and effective, and seemed free of any exogenous agents, the need to purify the vaccine proteins from the serum of hepatitis B-infected individuals was problematic. The advent of technologies to produce cloned, recombinant proteins for immunization purposes led to the discontinuation of this product in favor of a recombinant vaccine. This vaccine was based on expression of a cloned recombinant form of hepatitis B surface antigen (HBsAg), expressed in the yeast *Saccharomyces cerevisiae*. A variety of manufacturers currently market licensed hepatitis B vaccines. These are recommended as universal vaccines for all newborns, administered by intramuscular route at 0, 1, and 6 months

of age. Individuals who miss immunization in infancy should be vaccinated with a three-dose series as soon as is feasible. Some manufacturers will provide hepatitis B vaccine as a component of a "mixture" of other common childhood vaccines, to help minimize the total number of required injections. The vaccine is adjuvanted with aluminum hydroxide. The mechanism of action of vaccination appears to be the induction of IgG antibodies targeting the HBsAg, with an antibody response of at least 10 mIU ml^{-1} standing as a serological correlate of protection.

Human papillomavirus vaccine

Human papillomaviruses (HPVs) are common: there are at least 180 HPV genotypes described to date (Stanley, 2012). They are small, single-stranded, nonenveloped viruses that have a predilection for infection at mucosal or cutaneous surfaces. Most infections are asymptomatic, although many serotypes are associated with benign epithelial proliferation leading to warts. The major medical significance of HPV, however, stems from the fact that some subtypes are causally associated with malignancies of the anogenital track, particularly cervical carcinoma. Head and neck malignancies, respiratory papillomatosis, and anogenital warts are also caused by HPV infection. Worldwide, there are estimated to be approximately 530,000 new cases of HPV-associated cervical cancer per year, and 275,000 deaths (Tay, 2012).

There are approximately 15 HPV types that have been associated with anogenital malignancies; of these, HPV16 and HPV18 are the most prevalent, causing about 70% of cervical and anogenital cancer cases worldwide (Bosch et al., 2008). HPV6 and HPV11 are the types most commonly associated with genital warts (Lacey et al., 2006). There are two HPV vaccines currently licensed for clinical use. Both vaccines are based on the approach of generating noninfectious "virus-like particles" (VRPs) using recombinant technologies to express HPV proteins, which then spontaneously assemble into VRPs (Wang and Roden, 2013). The first licensed vaccine in the United States was a quadrivalent vaccine, based on VRPs cloned using recombinant technologies and synthesized in *S. cerevisiae*, and corresponding to HPVs 6, 11, 16, and 18. This vaccine is mixed with an aluminum hydroxide-based adjuvant prior to administration. The other licensed HPV vaccine is a bivalent vaccine, made up of VRPs corresponding to HPV16 and HPV18, and expressed in a recombinant baculovirus system prior to mixing with a monophosphoryl-lipid A-derived adjuvant. Both vaccines are extraordinarily effective at preventing HPV-associated malignancies as well as urogenital warts. The vaccines are administered by the intramuscular route, in a three-dose series commencing at age 9 years. The quadrivalent vaccine is currently recommended for boys and girls, whereas the bivalent vaccine (containing only the HPV types associated with cervical cancer) is recommended for girls only. The mechanism of protective immunity appears to be the induction of IgG antibody. The recent observation that there is cross-protective immunity induced by vaccination against nonvaccine strains provides optimism that these vaccines will protect against disease caused by diverse HPV types (Draper et al., 2013).

Inactivated influenza vaccine

Subunit, killed influenza virus vaccines have been in use for many decades in the United States. These vaccines are based on formalin inactivation of influenza viruses cultivated in fertilized eggs. Since the inactivation process kills the flu virus, it is impossible (and biologically inconceivable) that an individual could "get the flu" by being immunized. Typically, three strains are selected for cultivation (two strains of influenza A and one strain of influenza B), depending upon what strains have been observed circulating in the human population in recent outbreaks. Following formalin inactivation, enriched components of the virion are purified, and these so-called "split virion" component vaccines are administered in a single intramuscular injection annually prior to the onset of influenza season. Recently, an increasing number of pharmaceutical manufacturers have produced and marketed inactivated influenza vaccines. Some recent innovative vaccines that have either been licensed or are approaching licensure include vaccines manufactured in cell culture, rather than eggs, to avoid the issue of egg allergy (Brokhof et al., 2013); quadrivalent influenza vaccines capable of providing protection against two strains of influenza B in addition to two strains of influenza A (Ambrose and Levin, 2012); vaccines containing antigens generated using cloned, recombinant technologies (Sedova et al., 2012); vaccines using adjuvants to enhance the potency and effectiveness of influenza immunogens (Even-Or et al., 2013); and the development of vaccines expressing influenza immunogens as mRNA vaccines, analogous to the success that has been realized by COVID-19 mRNA vaccines (Scorza and Pardi, 2018). Given the disappointing performance of the past generations of influenza vaccines in controlling annual disease outbreaks (Osterholm et al., 2012), such advances and improvements are greatly needed (Atmar and Keitel, 2020).

Inactivated polio vaccine

As noted earlier in the section on oral, live, attenuated polio vaccines, the killed, inactivated IPV was actually the first vaccine against polio infection licensed in the United States (Melnick, 1996). The Salk vaccine was licensed in 1955, and the impact was immediate and dramatic. The total annual number of polio cases fell from 35,000 in 1953 to only 161 cases in 1961 (Hinman, 1984). In spite of this success, IPV was replaced by OPV in the early 1960s, due to the added benefits conferred by contact immunity, ease of administration (oral vs intramuscular), and lower cost. When it became clear by the 1990s that there was no longer any circulating wild-type poliovirus in the United States, and in fact that the only paralytic polio observed was VAPP caused by neurorevertant OPV, IPV once again became the vaccine of choice.

The IPV vaccine is administered by intramuscular or subcutaneous route. A four-dose series in childhood is recommended. There is no intestinal or mucosal immunity to IPV, in contrast to OPV. The mechanism of action is the induction of IgG antibodies capable of neutralizing the virus and protecting the central nervous system against paralytic polio. There is no contact immunity conferred by IPV immunization, although both IPV and OPV can produce "herd immunity" in a population if vaccination compliance is sufficient.

COVID-19 vaccines

The advent of the COVID-19 pandemic necessitated an urgent response, toward the goal of developing an effective vaccine against the SARS-CoV-2 virus. In response to this global crisis, a wide range of vaccine candidates have been developed. These range from nucleic acid based vaccines (DNA and RNA vaccines); live, attenuated vaccines; protein subunit vaccines; and vectored vaccines (Fiolet et al., 2021). In the United States, three vaccines have been licensed: two of these, BNT162b2 and mRNA-1273, are lipidated nanoparticle mRNA vaccines targeting the SARS-CoV-2 "Spike" protein, whereas the third vaccine, Ad26.COV2.S COVID-19, delivers the Spike open reading frame in the context of a replication-incompetent Adenovirus 26 vector. These vaccines have been remarkably effective in reducing COVID-19 infection, disease, hospitalization, and mortality. A major challenge for the future will be to continue to update vaccine design in response to emerging COVID-19 variants, such as the B.1.617.2 (Delta) SARS-CoV-2 variant (Cosar et al., 2021) and the B.1.1.529 (Omicron) variant (Saxena et al., 2021).

Viral vaccines and vaccine safety

In recent years, considerable attention has been given to the concern that vaccines, particularly the live, attenuated MMR vaccine, might be related to the development of autism in young children. Autism is a pervasive developmental disorder characterized by impaired social interaction, difficulties with verbal and nonverbal communication, and oftentimes stereotypical, repetitive patterns of behavior. It has become clear over recent years that the reports linking the MMR vaccine to autism were the product of flagrant scientific misconduct and clear-cut fraud (Flaherty, 2011). MMR and other vaccines have been demonstrated repeatedly to be safe and effective and no causal links have been found, in spite of exhaustive study, to link any childhood vaccine to autism or autism spectrum disorders (Gerber and Offit, 2009). A popular argument of the antivaccine movement is that the advent of new vaccines has created a state of "immune system overload" in children, by exposing them to too many antigens, too early in life. However, both the biological implausibility of this statement, as well as the fact that children today are in fact exposed to fewer total antigens in vaccines than they were in the 1960s (Offit et al., 2002), make this hypothesis completely untenable. Of even greater concern is the misinformation that has been promulgated about the safety of COVID-19 vaccines. Vaccine misinformation has contributed significantly to vaccine under-utilization, and this in turn has contributed to the sustenance of the COVID-19 pandemic globally (Ullah et al., 2021).

Priorities for new viral vaccines

Antiviral vaccines represent one of the most striking "success stories" in the history of medicine, having reduced (and in the case of smallpox, eliminated) the threat of many common, disabling, and even fatal virus infections. However, the vaccine armamentarium against serious viral infections is woefully incomplete and much work remains to be done. After the urgent need for continued optimization and implementation of COVID-19 vaccines, arguably the next most important – but to date elusive – target for vaccine development among viral infections is a vaccine for HIV, which continues to extract high levels of mortality in much of the world (Voronin et al., 2010). The most common vector-borne viral disease in the world is Dengue Fever, an infection that causes considerable morbidity and mortality, particularly in children. Although a Dengue vaccine has been licensed, its use is problematic (Wang et al., 2021). Prevention of dengue infection is a high priority for antiviral vaccine development (Lim et al., 2013). Hepatitis C infection is a common cause of liver failure as well as liver cancer, and a vaccine against this virus would represent an important public health advance (Voronin et al., 2010). Congenital infection (infection acquired by the developing fetus before birth) with cytomegalovirus is the most common infectious cause of birth defects, including hearing loss and developmental delay, in the United States. Development of a vaccine against this virus has therefore been designated as a major public health priority (Sung and Schleiss, 2010; Schleiss et al., 2017). Improved vaccines for influenza are needed, and a vaccine against respiratory syncytial virus is a high priority. This list is by no means exhaustive, but only serves to highlight a few of the many virus infections for which vaccines are still needed. In addition to these pathogens that require novel vaccines, improved vaccine delivery technologies are required. Vectored approaches, such as those offered by modified Vaccinia Virus Ankara and recombinant Vesicular Stomatitis Virus, are in clinical trials, and results are eagerly awaited. Nanoparticle vaccines also hold promise for improving immune responses for many "difficult" viral pathogens. Finally, scientists and clinicians need to be zealous advocates for immunization programs, in order to combat the untruthful agenda of the various organized antivaccine organizations. The field of antiviral vaccines greatly needs financial resources (Lindley et al., 2009), both from industry and government funding agencies, and more importantly the commitment of young investigators interested in research that will provide a tremendous "return on investment" in promoting the health of the population for future generations.

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Relevant websites

http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html— CDC.
http://immunizationinfo.org—Immunization information.