Chapter 1

Clinical Impact of Vaccine Development

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Abstract

The discovery and development of immunization has been a singular improvement in the health of mankind. This chapter reviews currently available vaccines, their historical development, and impact on public health. Specific mention is made in regard to the challenges and pursuit of a vaccine for the human immunodeficiency virus as well as the unfounded link between autism and measles vaccination.

Key words Vaccination, Immunization, Vaccine development, Public health, History of medicine

1 Introduction

Vaccination (Latin; *vacca*: cow) and sanitation have saved more lives and improved the public's health than any other medical intervention. Even before the germ theory of disease was established artificial induction was practiced in Asia and Europe [1]. Variolation, the process of obtaining pus from a smallpox vesicle and introducing it into the skin of an uninfected patient, was performed by people in various regions of Asia in the 1500s. This practice was observed by Lady Mary Wortley Montagu in Istanbul and introduced by her to England in 1721. Variolation, while effective, was not reliable and carried the real risk of developing smallpox from the process.

In 1774 an English farmer, Benjamin Jesty, noted that he was immune to smallpox after becoming infected with cowpox; subsequently, he successfully inoculated his wife and children and they were protected from smallpox as well. In 1798, Edward Jenner proved that large-scale inoculation with cowpox was an effective means of combating smallpox. In 1880, Louis Pasteur published work demonstrating that an attenuated form of the bacteria, *Pasteurella multocida*, could be used to produce a protective vaccine in animals. The following year, Pasteur's public demonstration of the effectiveness of an anthrax vaccine in sheep marked the beginning of a new era; it was now possible that vaccines could be reliably produced in a standardized, repeatable fashion.

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The history of vaccination, however, has not been without missteps or controversy. Early vaccines contained cells and bodily fluids and there was the legitimate concern that other infections could be transmitted through vaccination; the use of glycerin reduced this risk. The concept of introducing an infectious agent into healthy persons has been met with resistance from the start. For a time variolation was a felony crime in England. When Pasteur's rabies vaccine saved the life of Joseph Meister there was a public outcry in response to the process of purposefully injecting a lethal pathogen into a human—even one who was suffering from a uniformly fatal disease. The 1955 Cutter Incident, in which recipients of killed polio vaccine developed clinical disease due to the presence of live virus, resulted in 40,000 cases of vaccine-associated abortive polio, 164 cases of paralysis, and 10 deaths [2]. A 1998 Lancet paper by Andrew Wakefield that proposed a link between the measles-mumps-rubella vaccine and autism led to a widespread public loss of confidence in vaccines. The paper was subsequently found to be fraudulent and was withdrawn by the Lancet [3, 4]; however this, combined with the disproven theory that the thimerosal preservative in vaccines caused autism, continues to erode the public's confidence in vaccination [5].

Despite the unquestioned effectiveness and safety of vaccinations there continues to be groups of individuals who eschew vaccination for various scientific and religious beliefs. In the developing world, vaccination rates remain low for many contagious diseases. Until vaccination rates in both of these groups are increased the effectiveness of even the best designed vaccines will be limited and the public will remain at risk. In the following sections we review major vaccine-preventable diseases and the clinical impact that vaccination has had upon them.

2 Adenovirus Vaccines

Human adenoviruses are large, icosahedral, double-stranded DNA viruses belonging to family *Adenoviridae* [6]. They are further classified into seven species (A–G) and 52 serotypes. The history of *Adenoviruses* dates back to the 1950s when they were identified as a common cause for respiratory disease in children and US military trainees [7, 8]. In 1960s, the viruses caused significant morbidity and mortality among US military trainees.

Adenoviruses are spread primarily by respiratory droplets, fecooral route [9], or via direct contact. Close crowding promotes spread of virus. High-risk groups include children in day care centers and military trainees. Clinical syndromes associated with adenovirus infections in humans include respiratory adenovirus in children, acute respiratory disease (ARD) in military recruits, epidemic keratoconjunctivitis, pharyngoconjunctival fever,

hemorrhagic cystitis, infantile gastroenteritis, encephalitis, and opportunistic like infections in immunocompromised humans. Currently, there are no evidence-based guidelines supporting any specific antiviral treatment or prophylaxis for adenoviral illness. The off-label use of ribavirin and cidofovir has produced mixed results in immunocompromised patients with severe life-threatening adenoviral disease.

The first adenovirus vaccine was developed at the Walter Reed Army Institute of Research in 1956. It was an inactivated [10], injectable vaccine that protected against adenovirus infections caused by types 4 and 7. Production of this vaccine was terminated due to manufacturing issues. In 1971, Wyeth Laboratories developed live, oral enteric coated vaccines for adenovirus types 4 and 7. The rates of ARD dramatically reduced in the vaccine era. Unfortunately, the successful immunization program ended in 1999. Increasing mortality from adenovirus ARD in the postvaccination era resulted in the resumption of vaccine production for the military. Ad4 and Ad7 enteric coated live oral vaccines were reintroduced by Teva in 2011.

The CDC recommends two oral tablets to be swallowed [11], one tablet of adenovirus type 4 and one tablet of adenovirus type 7, as part of immunization schedule to military recruits, aged 17–50, who are beginning basic training. The most common side effects include nasal congestion, headache, upper respiratory infections, nausea, vomiting, and diarrhea. This vaccine is contraindicated in pregnancy and in those with anaphylaxis to vaccine components. Adenovirus vaccine in addition to secondary preventive measures including frequent hand washing, reducing crowded conditions, and cohorting has shown considerable reduction in ARD rates. A cost–benefit analysis estimated prevention of 4555 cases and $2.6 million savings with year-round vaccination [12]. Clinical trials have shown 94.5 % seroconversion, 99.3 % efficacy with Ad4 vaccine, and 93.8 % with Ad7 vaccine [13].

3 Anthrax Vaccines

Anthrax is a zoonotic disease caused by a spore-forming gram-positive bacilli *Bacillus anthracis* found in the soil. Human disease presents in three distinct clinical forms: cutaneous, inhalational, and gastrointestinal anthrax [14]. Injectional anthrax has also been described in intravenous heroin users [15]. Additionally, *Bacillus anthracis* is a Category A agent of bioterrorism.

Historically, researchers believe that anthrax originated in Egypt in 1250 BC and was responsible for the fifth and sixth biblical plagues. Clinically the disease was first described in the 1700s. In 1877, the German microbiologist, Robert Koch, studied *Bacillus anthracis* and described the causal relationship between

this specific bacterium and anthrax. In 1881, Louis Pasteur created the first vaccine using an attenuated strain of anthrax bacteria. Human anthrax was reported worldwide in the 1900s with industrial cases arising in developed countries and agricultural cases in developing Asian and African countries. With the advent of the first animal vaccine by Max Sterne in 1937 the number of human cases of anthrax dwindled. The first human vaccine against anthrax was created in the 1950s. Even though the incidence of human disease remains low, the use of *Bacillus anthracis* as a biologic weapon created the driving force for an improved human vaccine.

Anthrax is rare in the USA owing to vaccinations of livestock but remains common in developing countries that lack animal vaccination programs [16]. The bacterium produces highly resistant spores that can survive extreme environmental conditions for prolonged periods of time. The pathogenesis of disease in humans is attributed to the virulence factor of the capsule and production of two exotoxins. The anthrax toxin has three components—protective antigen (PA), lethal factor (LF), and edema factor (EF). The protective antigen with the edema factor forms the anthrax edema toxin responsible for cyclic AMP-mediated tissue swelling either in skin or mediastinum. The protective antigen with the lethal factor forms the anthrax lethal toxin responsible for cell death.

All three clinical presentations of anthrax have an incubation period of approximately 2–5 days. The cutaneous form of anthrax initially presents as a small, painless, pruritic papule that subsequently develops into a 1–2 cm large fluid-filled vesicle associated with surrounding edema, erythema, regional lymphadenopathy, and mild systemic symptoms. The vesicle ruptures in 5–7 days leaving behind an ulcer with black eschar which eventually falls off without a scar in 2–3 weeks. Antibiotics do not alter the development of cutaneous lesion. Inhalational anthrax manifests with nonspecific symptoms of myalgias, fever, and upper respiratory infection within 1–5 days of inhalation of infectious doses of *B. anthracis.* Patients then acutely develop respiratory distress syndrome from pulmonary hemorrhage and edema, and may die within 24 h. Widening of the mediastinum is a classic radiographic finding that develops secondary to lymphatic and vascular obstruction. If left untreated inhalational anthrax is 100 % fatal. Gastrointestinal anthrax develops after ingestion of anthrax-infected meat. Symptoms include abdominal pain, nausea, vomiting, diarrhea, and hematemesis with progression to septic shock and death. All three primary forms of anthrax can also manifest with bacteremia and secondary meningitis. Anthrax does not spread from person to person. Treatment involves decontamination and use of antibiotics such as ciprofloxacin, doxycycline, and penicillin. Passive immunization with human monoclonal anti-PA antibody, raxibacumab, has been approved for use in inhalational anthrax.

The human anthrax vaccine, anthrax vaccine adsorbed (AVA), is produced from a cell-free culture filtrate of attenuated,

non-encapsulated strain V770-NPI-R of *B. anthracis*. It predominantly contains the protective antigen adsorbed to aluminum hydroxide. This vaccine is mainly recommended for certain members of the US military, laboratory workers who work with anthrax [17], and individuals who work with animal and animal products. The vaccine is an intramuscular injection given as five shots at 0 and 4 weeks and 6, 12, and 18 months with annual booster [17]. For postexposure prophylaxis [17], three injections of AVA at 0, 2, and 4 weeks plus 60 days of antibiotics have been recommended. Side effects of the vaccine include mild local reaction and nonspecific systemic symptoms such as low-grade fever, headache, and myalgia. The only contraindication is hypersensitivity to the vaccine. There have been no controlled clinical trials in humans to determine either the efficacy of AVA or its use along with antibiotics for postexposure prophylaxis. However the use of AVA has reduced the incidence of anthrax among industrial and agricultural workers.

4 Cholera Vaccines

Cholera is an acute diarrheal illness caused by the bacterium *Vibrio cholerae*. It is one of the oldest infectious diseases known to mankind. In the eighteenth century the disease spread from its original reservoir, the Ganges Delta in India, causing epidemics and pandemics resulting in the death of massive numbers of people across the globe.

Cholera is an intestinal infection with toxigenic strains of *V. cholerae* serogroups O1 and O139. *V. cholerae* O1 serogroup is further classified into two serotypes—Ogawa and Inaba—and two biotypes—classical and El Tor. The mode of transmission is through ingestion of contaminated food and water [18]. The disease occurs in children and adults especially in the lower socioeconomic groups. The short incubation period of 2 h to 5 days is responsible for exponential wave of this disease. Following consumption of infected food, the bacterium uses its virulence factors—toxin-coregulated pilus (TCP) [19], hemagglutinin [20], and single flagellum to colonize the small intestine and secretes cholera enterotoxin (CT). The "-B-" subunit of CT binds to the GM1 ganglioside receptor, facilitating entry into the intestinal mucosal cells and "-A-" subunit activates adenyl cyclase leading to excess fluid and salt secretion. Clinical symptoms include acute diarrhea and vomiting rapidly leading to electrolyte imbalances, hypovolemic shock, multiorgan failure, and death. Cholera can be fatal if there is a delay in replacement of fluid and electrolytes. Diagnosis is made clinically and by identifying the bacterium in stool cultures. Serologic tests are available but are nonspecific.

The global annual incidence of cholera is uncertain but the approximate cases may be 3–5 million causing 100,000–120,000

deaths. More than half the cases occur in Africa and remainder in Asia. There have been sporadic cases along the US Gulf Coast associated with undercooked or contaminated seafood. The majority of other cases in the developed countries are secondary to travel to endemic areas.

The preparation of the earliest vaccine against cholera began in the late eighteenth century. Initial studies were made with a parenteral killed whole-cell cholera vaccine in the 1880s which had limited use owing to short-term efficacy. The currently licensed cholera vaccines contain either genetically attenuated strains, killed organisms, or antigens. Three oral vaccines—two killed and one live—have been developed and licensed in several countries. The whole-cell killed vaccine plus CTB (WC-rCTB/Dukoral) contains killed strains of *V. cholerae* O1 (classical, El Tor, Ogawa, and Inaba) with B subunit of cholera toxin. The vaccine is given as two oral doses combined with a liquid oral buffer, 7–14 days apart in adults and in three doses in children 2–6 years of age with need for further booster doses. The vaccine is WHO prequalified but remains experimental in the USA. The reformulated bivalent killed whole-cell-only vaccine (WC-only/Shancol in India/mORCVAX in Vietnam) contains killed whole cells of *V. cholerae* O1 and O139. It is given as two doses 2 weeks apart with further boosters at 3-year intervals. Since the vaccine does not contain the gastric acid-labile cholera toxin subunit, it does not have to be coadministered with a buffer. The only live oral cholera vaccine is CVD103-HgR (Orochol or Mutachol). The vaccine is a live attenuated Inaba strain, which is genetically engineered to express CTB subunit and not the active CTA subunit. The vaccine is administered as a single oral dose with a buffer and does not require booster doses. The live vaccine has not been prequalified by WHO.

The WHO recommends the use of the two killed oral vaccines in cholera endemic areas and areas at risk for outbreaks [21]. The cholera vaccine is unavailable in the USA and CDC does not recommend cholera vaccines to most travelers owing to short-term and incomplete protection. These vaccines however cannot replace the pivotal role played by hygiene and proper sanitation in the control of cholera outbreaks.

5 Diphtheria Toxoid

Diphtheria is an acute toxin-mediated disease caused by *Corynebacterium diphtheriae*, a gram-positive bacillus that is acquired via the respiratory tract. The disease has been well described throughout history with Hippocrates famously writing about it in the fifthcentury BC. Outbreaks throughout Europe occurred as early as the fifteenth century. Spain experienced a major epidemic, in 1613, known as "El Año de los garrotillos," the year of strangulation [22].

Corynebacterium diphtheriae is a toxin-producing gram-positive bacillus. It has three biotypes: gravis, intermedius, and mitis, with the most severe forms of disease being produced by the gravis serotype. Susceptible persons may acquire toxigenic bacillus in the nasopharynx. The organism produces a toxin that inhibits protein synthesis and is responsible for local tissue disease and membrane formation. The locally produced toxin is absorbed into the bloodstream and transferred to other tissues.

The clinical presentation of diphtheria can be insidious with an incubation period of 1–5 days. Usually the symptoms are nonspecific and mild in the initial stages with fever and mild pharyngeal erythema being common. Within 3–4 days patches of exudate appear that coalesce to form membranes covering the entire pharynx [22]. As the disease progresses, large adenopathies become evident and patients begin to appear toxic. Attempts to remove the membranes often result in bleeding. Patients may recover following this stage. If enough toxin has been produced, patients may develop acute disease with prostration, coma, and high fevers. Marked edema and adenopathy may result in the classic "bullneck" appearance. Although pharyngeal diphtheria is the most common form of the disease in unimmunized populations, other skin or mucosal sites may be involved. This includes the nasopharynx, cutaneous, vaginal, and conjunctival forms. Invasive disease is very rare and is due to nontoxigenic strains of *C. diphtheriae*. Most complications of diphtheria, including death, are attributable to the toxin. Myocarditis can occur early in the disease process or appear weeks later. When it does occur, it is often fatal. Neuritis often affects motor nerves and can cause pharyngeal paralysis. The overall mortality of diphtheria is 5–10 % with rates as high as 20 % in those younger than 5 years or older than 40 [22].

Diphtheria antitoxin produced from horses was first used in the USA in 1891 and it was commercially produced in Germany in 1892. Equine diphtheria antitoxin is produced by hyperimmunizing horses with diphtheria toxoid and toxin. To prevent reactivity from horse serum, current preparations are semi-purified by techniques that concentrate IgG and remove as much extraneous proteins as possible. Diphtheria antitoxin is used for the treatment of infected patients and, in the past, for persons with high-level exposures.

The development of an effective toxoid, a combination of toxin-antitoxin, was achieved in the 1920s. Beginning in the 1940s, this was combined with the pertussis vaccine and became widely used. Diphtheria toxoid is produced by growing toxigenic *C. diphtheriae* in liquid medium. The filtrate is incubated with formaldehyde to convert toxin to toxoid and is then adsorbed onto an aluminum salt. Diphtheria toxoid is available combined with tetanus toxoid as pediatric diphtheria-tetanus toxoid (DT) or adult tetanus-diphtheria (Td), and with both tetanus toxoid and acellular pertussis vaccine as DTaP and Tdap. Diphtheria toxoid is also

available as combined DTaP-HepB-IPV (Pediarix) and DTaP-IPV/Hib (Pentacel) [23].

After a primary series of three properly spaced diphtheria toxoid doses in adults or four doses in infants, a protective level of antitoxin (defined as greater than 0.1 IU of antitoxin/mL) is reached in more than 95 %. Diphtheria toxoid has been estimated to have a clinical efficacy of 97 % [2]. Revaccination is recommended every 10 years.

6 Haemophilus Influenza Vaccines

Haemophilus influenzae is an important cause of severe bacterial infections in children younger than 5 years. It was first identified by Koch in 1883 but it was not until the influenza pandemic in 1918 that *H. influenzae* was recognized as a cause for secondary infection and not the primary cause of influenza [24]. In 1931, Pittman [25] demonstrated two categories of *H. influenzae*-encapsulated and nonencapsulated forms and further designated six serotypes (a–f) [25] on the basis of capsular properties. *H. influenzae* type b (Hib) was responsible for 95 % [26] serious invasive bacterial infections in the prevaccine era.

Haemophilus influenzae is an aerobic, non-spore-forming gram-negative coccobacillus. It requires two factors "X" (hemin) and "V" (nicotinamide adenine dinucleotide) [27] for in vitro growth, a property that distinguishes it from other *Haemophilus* species. The polyribosyl-ribitol-phosphate polysaccharide capsule is responsible for virulence and immunity. Hib colonizes nasopharynx (asymptomatic carriers) and is spread through respiratory droplets. Antecedent viral infections may play a role in invasive disease. Common invasive presentations include meningitis, pneumonia, otitis media, epiglottitis, septicemia, cellulitis, and osteoarticular infections. Non-type-b-encapsulated *H. influenzae* rarely causes invasive disease. A positive culture of *H. influenzae* from infected sterile body fluid or detection of Hib polysaccharide antigen in CSF is diagnostic. Serotyping is extremely important as type b isolated in children younger than 15 years is a potentially vaccine-preventable disease.

The first-generation pure polysaccharide vaccine (HbPV) was introduced in the early 1980s in the USA but was not immunogenic in children younger than 18 months and had variable efficiency in older children (age-dependent vaccine response). It was used until 1988 and is no longer available in the USA. The conjugation of the polysaccharide to the "carrier" protein results in a T-dependent antigen and increases immunogenicity and boosts response. The annual incidence of invasive Hib disease before the use of conjugate vaccine was 20–88 cases per 100,000 cases in the USA and has dramatically reduced ever since its introduction. Four conjugate Hib vaccines have

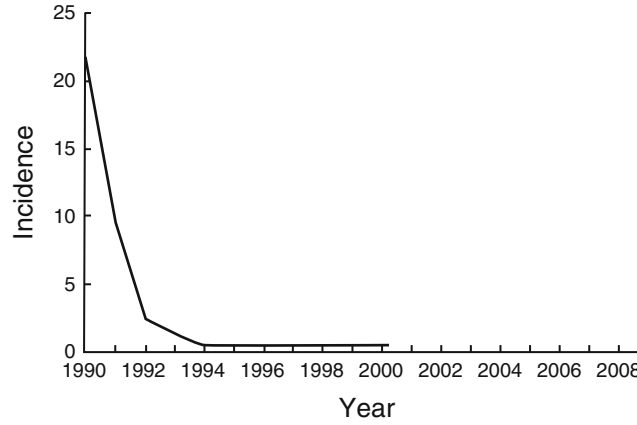

Fig. 1 Incidence of invasive Hib disease 1990–2009 (rate per 100,000 children less than 5 years of age). Graph from CDC/vaccines/pinkbook/hib

been developed [28]. The first *H. influenzae* type b polysaccharide-protein conjugate vaccine (PRP-diphtheria toxoid conjugate) was licensed in 1987 and is no longer available. The Haemophilus b oligosaccharide conjugate (HbOC) licensed in 1990 contains oligosaccharides from purified PRP from Hib Eagan strain coupled with nontoxic variant of diphtheria toxin isolated by *Corynebacterium diphtheriae*. The PRP-OMP vaccine was also licensed in 1990 and is a purified PRP from Hib Ross strain covalently bonded to an outer membrane protein complex of *Neisseria meningitides* strain B11. PRP-T is covalently bound PRP to tetanus toxoid and was licensed in 1993. The three HiB conjugate vaccines licensed for use are interchangeable. The Advisory Committee on Immunization Practices (ACIP) recommends start of immunization as early as 6 weeks of age with total of three doses of any combination HiB vaccines before the first birthday and a booster dose at 12–15 months of age. The only contraindication is hypersensitivity to vaccine components. HiB is not routinely recommended for persons 5 years and older; it can be considered in special situations such as asplenia, sickle cell anemia, or HIV infection (Fig. 1).

The routine use of HiB conjugate vaccine has dramatically decreased disease in developed countries and shown to be highly effective in reducing the incidence of disease in developing countries. Efforts are under way by the WHO to increase awareness and global availability of this effective vaccine especially in resource-limited countries.

7 Hepatitis A Vaccines

The first description of hepatitis or "episodic jaundice" dates back to the time of Hippocrates, and the earliest outbreaks were reported in Europe in the seventeenth and eighteenth centuries [29].

During World War II the scientific details regarding this disease were obtained. Hepatitis A was epidemiologically differentiated from hepatitis B in 1940s but it was only in 1970s that serological tests were developed to definitively diagnose this disease.

Hepatitis A occurs worldwide but is endemic in Central, South America, Asia, the Middle East, and Africa. It is caused by *hepatitis A virus (HAV)*, a non-enveloped RNA virus belonging to the family of *Picronaviridae*. Humans are the only natural host. HAV is resistant to most organic solvents and detergents and can survive at a pH as low as 3 but can be inactivated by high temperature (>85 °C), chlorine, and formalin [30]. *HAV* infection is acquired through fecal-oral route either by person-person contact or through ingestion of contaminated food or water. The incubation period is approximately 28 days [31]. *HAV* replicates in the liver; infected persons shed the virus for 1–3 weeks and have a very high risk of transmission 1–2 weeks prior to the onset of symptoms. Risk factors for *HAV* infection include international traveling, men who have sex with men, intravenous drug users, and persons with chronic liver disease or with clotting disorders. The clinical features are similar to other types of acute viral hepatitis. HAV infection presents as an acute febrile illness with nausea, abdominal discomfort, and jaundice. Other atypical manifestations include vasculitis, cryoglobulinemia, and neurologic, renal, and immunologic reactions. HAV is a self-limited disease that does not produce chronic infection or chronic liver disease. Fatality from acute liver failure occurs in 0.5 % of those infected. Diagnosis is made on clinical, epidemiologic, and serologic basis. The antibody test for total anti-HAV measures both IgM-HAV and IgG-HAV. IgM becomes positive in acute HAV infection within 5–10 days before the onset of symptoms and can persist up to 5–6 months. IgG appears in the convalescent phase of the disease and confers lifelong protection.

In the prevaccine era, the only methods for prevention of hepatitis A were hygienic measures and use of protective immunoglobulins. Two inactivated whole-virus hepatitis A vaccines, VAQTA and HAVRIX [32, 33], were licensed in 1995 in the USA and approved for use. The other vaccines used worldwide are AVAXIM, EPAXAL, and Heavile. All these vaccines are made from different strains of the HAV; VAQTA is based on strain CR326F, and HAVRIX is based on strain HM175 and contains a preservative unlike VAQTA. Both vaccines are highly immunogenic. ACIP recommends vaccination for all children at 12–23 months of age. Adults who are at increased risk of infection or complication from HAV infection should be routinely vaccinated. HAVRIX is administered intramuscularly as a single primary dose in children 1–18 years (0.5 ml) and adults above 19 years (1 ml) followed by a booster at 6–12 months. VAQTA is administered similarly to HAVRIX; however the booster is administered 6–18 months after primary dose. In 2001, Twinrix—a combination vaccine with adult dose of hepatitis B vaccine (Engerix-B)

and pediatric dose of HAVRIX—was approved for adults greater than 18 years of age; it is given intramuscularly at 0, 1, and 6 months. Contraindications to the vaccine include allergic reactions or moderate-to-severe illness. Adverse reactions include pain at injection site but systemic side effects are rare. The wide use of vaccines has resulted in a sustained reduction of disease in most of the developed world; however hepatitis A infection remains an ongoing issue in the developing world.

8 Hepatitis B Vaccines

Hepatitis has been recognized as a clinical entity since the times of Hippocrates when he dubbed it epidemic jaundice. However, the wide diversity of viruses that can be responsible for this entity has only recently begun to be recognized. The first case of "serum hepatitis" or what was believed to be hepatitis B was first described during an epidemic which resulted from vaccination against smallpox in shipyard workers in late nineteenth-century Germany. Jaundice developed in 15 % of the inoculated workers. The role of blood as a vehicle became clearer in 1943 when Beeson described the transmission of hepatitis to recipients of blood transfusions [34].

Hepatitis B virus is a small double-shelled DNA virus of the family *Hepadnaviridae* [34]. It has a small circular DNA genome. It contains several antigens including the hepatitis B surface antigen, hepatitis B core antigen, and the hepatitis B E antigen. Humans are the only known host to the virus.

Hepatitis B virus is primarily hepatotropic; although hepatitis B surface antigen (HbSAg) has been recovered from other organs, there is little evidence that it replicates outside of the liver. Most experimental data supports the notion that the virus is not directly cytopathic but rather the damage to tissue is mediated by an immune response to the virally infected hepatic cells. Infection can range from being asymptomatic to causing a fulminant hepatitis. Persons infected with hepatitis B can also progress to a chronic infection resulting in cirrhosis and hepatocellular carcinoma [34].

The clinical course of hepatitis B is indistinguishable from other causes of viral hepatitis. The incubation period ranges from 40 to 160 days. Definitive diagnosis requires serological assays to distinguish it from other causes of hepatitis. The preicteric phase which occurs a week before the onset of jaundice is characterized by malaise, fatigue, nausea, vomiting, and right upper quadrant pain. The icteric phase lasts from 1 to 3 weeks and is characterized by jaundice, hepatomegaly, and acholia. Approximately 40 % of people in the USA that develop acute hepatitis B are hospitalized. Fulminant hepatitis occurs in 0.5–1 % of cases and is more common in adults than children. During the convalescent phase, all symptoms resolve but fatigue may linger for weeks.

Approximately 5 % of cases will progress to chronic infection with the risk of chronic infection decreasing with age. As many as 90 % of infants who acquire the virus from their mothers progress on to chronic infection. Persistent infection is defined as having a positive HBSAg for more than 6 months. Viral replication persists throughout the course of chronic hepatitis B infection and disease progression depends on interactions between the virus and host immunity. It is a dynamic process that may span over the course of decades. Most patients can be asymptomatic but continue to spread infection. This carries a 25 % risk of developing cirrhosis and dying of liver cancer.

The incidence of hepatitis B peaked in the 1980s. Approximately 10,000 or less cases are now reported annually in the USA. Before routine childhood immunizations, most infections occurred in adults. The highest risk groups are those between 20 and 45, those who engage in high-risk sexual practices, and those who use injection drugs. Up to 16 % of patients who acquire the disease deny any risk factors [35].

Hepatitis B vaccine has been available in the USA since 1981. It consists of a 226-amino acid S gene product. This gene is injected via plasmids into *Saccharomyces cerevisiae* which produce a recombinant HbSAg protein. The final product contains 95 % purified protein surface antigen but no yeast DNA. Thus, infection cannot result from hepatitis B vaccination. The vaccine has a proven efficacy of around 90–95 % [35, 36] in normal populations with lower rates of immunogenicity in subsets of patients. A particularly challenging group has been patients with *HIV* in whom vaccine efficacy can be as low as 30 %. This is worrisome as patients with HIV are to be considered high risk for acquiring the infection [37].

9 Human Papillomavirus Vaccines

Human papillomavirus (HPV) is a DNA virus that causes epithelial lesions of mucous membranes ranging from benign papillomas to carcinoma [38–40]. The association of HPV and cancer was first described by Orth [41] in 1970s. In the 1980s, zur Hausen [42] identified HPV 16 and HPV 18 in cervical cancer cells. The introduction of screening and use of HPV vaccines have decreased the incidence of HPV-associated cervical cancers in the developed world [43]. However, the incidence of HPV-associated anal and oropharyngeal cancer is on the rise.

HPV is the most common sexually transmitted disease in the USA. It is estimated the prevalence varies from 14 to more than 90 %, the highest rate occurring in the age group 20–24. HPV is transmitted through vaginal sex, anal sex, genital-genital contact, and oral sex and rarely from pregnant women with genital HPV to their babies causing recurrent respiratory papillomatosis (RRP) in

the child. HPV replicates in the nuclei of stratified squamous epithelial cells. In majority of individuals HPV is spontaneously cleared but in small number of cases HPV persists with risk of progression to high-grade dysplasia or invasive carcinoma of the cervix, vulva, vagina, penis, anus, and oropharynx [44]. In the USA, there are approximately 17,000 women and 9000 men affected with HPV-related cancer yearly. The Pap smear used as a screening tool helps prevent HPV-associated cervical cancer in women but unfortunately the lack of screening for other HPV-related cancers results in increased morbidity and mortality.

There are two available HPV vaccines—Gardasil and Cervarix. Gardasil is a recombinant human papillomavirus quadrivalent vaccine produced in the yeast *Saccharomyces cerevisiae* [45]. It contains viruslike particles of types 6, 11, 16, and 18 which together cause around 90 % of genital warts. Cervix is a recombinant bivalent vaccine composed of viruslike particles of types 16 and 18, which causes approximately 70 % of cervical cancers worldwide. In young females, either of the vaccines may be used. The target age group is 9 through 26 years of age to prevent HPV-related genital warts, cervical intraepithelial neoplasia, and cancers. In young males, Gardasil is the only approved vaccine, with target age group being 11–12 years. HPV vaccination is also recommended for older teens who are not vaccinated when younger. Both HPV vaccines are administered intramuscularly as a three-dose schedule—with the second dose being given 1 or 2 months after the initial dose and third dose 6 months after the first dose. The vaccine series does not have to be restarted if interrupted and can be interchanged with either HPV vaccine product to complete series. The most commonly reported side effects are nausea, headache, dizziness, and local reactions at injection site. The vaccine is contraindicated in persons with history of hypersensitivity to vaccine components and in pregnancy owing to limited efficacy data. Its use is safe in immunocompromised hosts as both Gardasil and Cervarix are noninfectious vaccines.

Despite the safety and efficacy, HPV vaccines remain underutilized. It is estimated that only 57 % of adolescent girls and 35 % of adolescent boys received one or more doses of HPV vaccine. CDC data and statistics [46] illustrate that if clinicians give a stronger recommendation for adolescent HPV vaccinations before the age of 13, 91 % of adolescent girls would be protected from HPV-related cancers.

10 Influenza Vaccines

Influenza is a highly contagious viral disease caused by the single-stranded RNA *influenza virus*. Descriptions of pandemic influenza can be found in many places throughout history and its name is

derived from an epidemic in fifteenth-century Italy which was thought to have occurred under the influence of the stars [47]. At least four pandemics occurred in the nineteenth century and three occurred in the twentieth century. The infamous Spanish influenza which occurred in the early twentieth century was responsible for at least 18–19 million deaths which dwarfed World War I which was occurring at the time and may be partially responsible for ending that conflict. The virus itself was first isolated in the 1930s for the first time by Smith, Andrews, and Laidlaw. The first inactivated vaccine was first created in the 1950s and that was followed by a live attenuated vaccine in 2003.

Influenza virus is a single-stranded RNA virus of the family *orthomyxovirus* [47]. Basic antigen types A, B, and C are determined by nuclear material. Influenza A can be further characterized by two components, hemagglutinin (H1, H2, and H3) and neuraminidase (N1, N2) which play roles in viral cell penetration. Influenza A naturally infects humans, swine, and poultry among other birds and the virus can freely exchange genetic material in these hosts. The H and N antigens vary and are part of the reason why the virus is so successful at evading immunity and the reason vaccines need to be reformulated annually. The virus undergoes antigenic drift which is a minor variation of its surface antigens caused by point mutations in a gene segment. These can result in epidemics since the protection that has been conferred by prior years of infection is incomplete. Antigenic shift on the other hand is a major change in one or both H and N antigens that are likely the result of a recombinant virus exchange between those who affect birds and humans. These major changes occur at varying intervals and are responsible for worldwide pandemics.

Following respiratory transmission, the virus proceeds to invade respiratory epithelial cells in the trachea and the bronchi. This replication itself results in cellular death. Of those infected, 30–50 % will not experience symptoms and those who go on to develop them can have a wide spectrum of manifestations ranging from mild respiratory complaints to a rapidly evolving febrile illness complicated by secondary bacterial infections [48]. Primary influenza is characterized by the abrupt onset of fever, chills, myalgias, headache, sore throat, and extreme fatigue. The presence of fever and respiratory symptoms are the most sensitive indicators of illness. Fever may range from 38 to 40 °C but may vary. Symptoms usually improve within 1 week but cough and fatigue can persist for 2 weeks or more. Gastrointestinal symptoms, croup, and otitis media can occur and are more common in children. Complications from influenza tend to occur in the extremes of age and those with comorbidities. The most common complications are exacerbations of underlying conditions such as COPD, congestive heart failure, and coronary artery disease. This is coupled with the development

of bacterial pneumonia caused by usual community pathogens as well as an increased incidence of *Staphylococcus aureus* pneumonia. In the USA influenza is responsible for over 200,000 hospitalizations and 30–5000 deaths annually with the largest impact on the elderly and the very young. A greater number of hospitalizations occur in years when influenza H2N3 is the predominant strain. An increase in mortality typically accompanies influenza epidemics and a large number of these deaths are not directly related to the infection but rather to its complications such as cardiac events and exacerbation of other chronic medical conditions.

Two types of influenza vaccines are currently available: an inactivated trivalent or quadrivalent vaccine containing influenza A H3N2 and H1N1 plus influenza B-inactivated viruses, and an attenuated live virus vaccine that has the equivalent components of the inactivated trivalent vaccine. The inactivated vaccine is injected intramuscularly or intradermally. Hemagglutinin is the main component and immunogen in these vaccines. In 2003 the FDA approved a live attenuated vaccine. It contains the same components of the trivalent inactivated vaccine; they are cold adapted and reproduce effectively in the nasopharynx of the recipient. It is administered as a single dose of a spray through each nostril.

The immunity conferred by the inactivated virus vaccine is deemed to last for less than a year. On years when there is a good match between the circulating strain and the vaccine, protection can be as high as 90 % among those younger than 65 and around 40 % in older patients [49, 50]. This usually yields a vaccine efficacy close to 50–60 %. Vaccination has also been shown to be effective at preventing complications of influenza. Inactivated vaccine should be administered on a yearly basis to eligible patients which now includes all patients older than 6 months.

The live attenuated virus vaccine is 87 % effective in decreasing disease and close to 30 % effective in decreasing otitis media. The live attenuated vaccine should be administered to patients older than 2 years up to age 49 [51].

Recommendations for the antigenic composition of the vaccines are made annually to ensure that the vaccines are effective against recently circulating strains of the virus. This is subject to antigenic drift and shift which explains why certain influenza seasons feature strains not anticipated by vaccine makers. The timeline for production of the vaccine is similar each year and hinges on the activity of the WHO influenza surveillance network. Because production of the vaccine requires several months, data collection must be balanced with manufacturing times. If recommendations are made too early, then antigens could change rendering the vaccine ineffective. If recommendations are made too late, timely vaccine manufacture may be impossible.

11 Japanese Encephalitis Vaccines

Japanese encephalitis (JE) is a vaccine-preventable mosquito-borne viral infection that occurs in the developing countries of Asia. Outbreaks consistent with JE were reported as far back in 1871 in Japan and the virus was first isolated from *Culex tritaeniorhynchus* in 1938.

JE virus (JEV) is a single-stranded RNA *flavivirus* closely related to West Nile and Saint Louis encephalitis virus. JEV is transmitted through the bite of infected Culex species of mosquitoes. The natural cycle of the JEV is enzootic consisting of bird-mosquito-bird or pig-mosquito-pig circulation of the virus. Humans are incidental or dead-end hosts. Human-to-human transmission is rare but cases from vertical transmission and through organ transplant have been reported. Transmission usually occurs in rural agricultural areas, mainly associated with irrigated rice fields in the tropical and temperate regions of eastern and southern Asia. Epidemic activity is highest in summer and early fall while endemic activity is sporadic and not associated with any seasonal pattern. JE is primarily a disease of children as adults acquire immunity through natural infection. As per the CDC, the incidence of JE among travelers to Asia from non-endemic areas is less than one case per million travelers [52].

The majority of human infections with JEV are asymptomatic with less than 1 % of developing clinical symptoms. The incubation period is 5–15 days. The most common presentation is that of acute encephalitis with sudden onset of fever, headache, vomiting, and mental status changes. Other manifestations include seizures, a parkinsonian syndrome, and acute flaccid paralysis [53] resembling poliomyelitis. IgM antibody of CSF and serum samples is currently the standard test for diagnosis. Viral isolation and nucleic acid amplification tests are insensitive tools for diagnosis. There is no specific treatment and therapy consists of supportive care and managing complications.

The incidence of JE has drastically decreased over the last few decades owing to vector control programs and vaccinations. The three most important types of vaccines currently used are purified, mouse brain-derived, inactivated Nakayama or Beijing strains of JEV; cell culture-derived inactivated JE vaccine based on Beijing P3 strain; and cell culture-derived live attenuated JE vaccine from SA 14-14-2 strain. The only licensed vaccine in the USA is the inactivated vero cell culture-derived vaccine branded as Ixiaro, approved in 2009. The ACIP recommends vaccination [54] for travelers spending more than 1 month in endemic areas during the JEV transmission season or short-term travelers with high risk or uncertain activities or traveling to a region with a JE outbreak. The primary immunization schedule includes two intramuscular

injections given on days 0 and 28 to be completed at least 1 week prior to travel date. There is limited data on efficacy and use in pregnancy. The common adverse reactions include local reaction and flu-like illness.

12 Meningococcal Vaccines

Meningococcal disease is an acute, potentially life-threatening disease caused by the gram-negative, endotoxin-producing bacteria *Neisseria meningitidis* or the meningococcus. It causes meningitis, sepsis, and focal infections. Epidemics of meningococcal meningitis were first described in the early eighteenth century. Prior to the advent of antibiotics, the case fatality rate was as high as 70–85 % (Fig. 2).

Meningococcus is an aerobic, gram-negative diplococcus and is a normal commensal of the human nasopharynx. The organism has an inner cytoplasmic membrane and outer membrane separated by a cell wall. The outer membrane proteins and polysaccharide capsule serve as antigens and are responsible for the pathogenicity of the organism. Meningococci are classified on the basis of characteristics of the polysaccharide capsules—at least 13 serogroups have been described and most invasive disease is caused by serogroups A, B, C, Y, and W-135.

The meningococcus colonizes only the nasopharynx and carriage rates are highest among adolescents and young adults [55–57]. It is transmitted through aerosol droplets or direct contact with respiratory secretions. Risk factors for infection include complement deficiency [58, 59], asplenia [60], HIV, recent viral illness, and tobacco smoking. In less than 1 % of colonized humans the organism invades to cause bacteremia and around 50 % of the bacteremic patients develop meningeal involvement. The incubation period is around 2–10 days. Clinical presentations include meningitis and bloodstream infections, called meningococcemia, characterized by fever, hypotension, petechial rash, and multiorgan failure. Less common manifestations include otitis media,

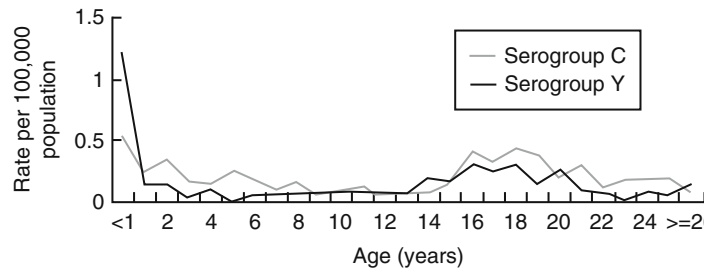

Fig. 2 Rates of meningococcal disease by age, USA, 1999–2008. Source: CDC/vaccines/meningococcal; CDC Active Bacterial Core Surveillance

pneumonia, and arthritis. Diagnosis is made by a positive gram stain and bacterial culture from a normally sterile site. Detection of polysaccharide antigen in CSF and serology may also be used in evaluation. Intravenous aqueous penicillin is considered therapy of choice.

Vaccination is the most effective method to prevent meningococcal disease. The first meningococcal polysaccharide vaccine (Menomune; MPSV4) was licensed in the USA in 1978 and is a quadrivalent A, C, Y, W-135 polysaccharide vaccine administered subcutaneously. Three meningococcal conjugate vaccines (MCV4-Menactra, Menveo, MenHibrix) are available in the USA. Menactra was licensed in 2005 [61, 62] and Menveo in 2010 [63]. Both vaccines are quadrivalent A, C, Y, W-135 conjugated to diphtheria toxoid, approved for persons 2–55 years of age. MenHibrix is a meningococcal serogroup C, Y, Haemophilus B tetanus toxoid conjugate vaccine. It is indicated to prevent meningococcal and Haemophilus disease in children 6 weeks through 18 months of age. The first meningococcal serogroup B vaccine available in the USA called Trumenba was licensed in late 2014 for individuals 10–25 years in a three-dose series at 0, 2, and 6 months. The vaccine is indicated [64] in persons aged 11–18 years, first dose at age 11–12 years and a booster at age 16 or first dose if given at 13–15 years then booster at 16–18 years. No booster is indicated if primary dose was given on or after age 16 years. Other indications [64] include persons aged 2–55 years or 9 months–2 years with functional or anatomical asplenia or complement deficiency, with increased risk for exposure or travel to hyperendemic areas. Bexsero, a second meningococcal serogroup B vaccine, was approved by the FDA in January 2015. It is administered in two doses 1 month apart. At the time of this writing, the CDC has not yet published recommendations on the use of the serogroup B vaccines; these recommendations are expected to be released in June 2015. Adverse reactions include local reactions, fever, and mild systemic symptoms. Contraindication [64] to the vaccine is moderate-severe illness or allergy to vaccine component. In most areas, invasive meningococcal disease is a reportable condition. Antimicrobial chemoprophylaxis (ciprofloxacin, rifampin, ceftriaxone) is recommended for close contacts with exposure to index patient given the high rate of secondary disease.

12.1 Measles, Mumps, and Rubella Vaccine

Measles is a ubiquitous, highly contagious disease caused by the measles virus. It was recognized as early as seventh century. Measles was described as severe disease, “more to be dreaded than smallpox”—for the first time by Persian physician Rhazes in the tenth century [65, 66]. In the pre-vaccine era, school-aged children had the highest risk of infection and more than 95 % of cases occurred by 15 years of age [67, 68] (Figs. 3, 4, and 5).

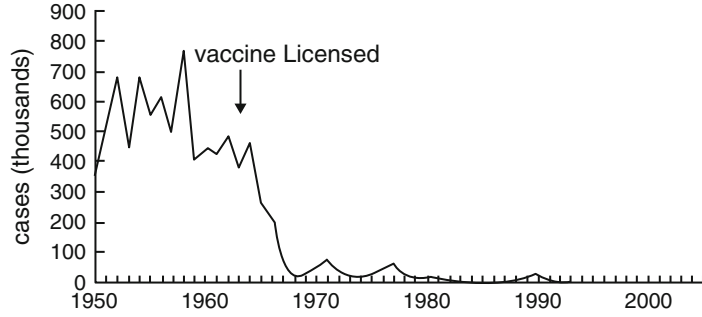

Fig. 3 Measles—USA, 1950–2009. Graph from CDC/vaccines/pinkbook/measles

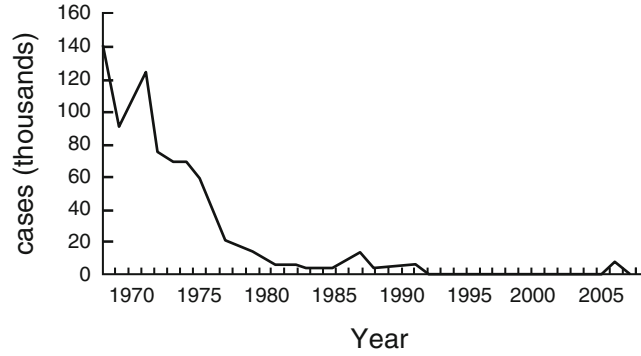

Fig. 4 Mumps—USA, 1968–2009. Graph from CDC/vaccines/pinkbook/mumps

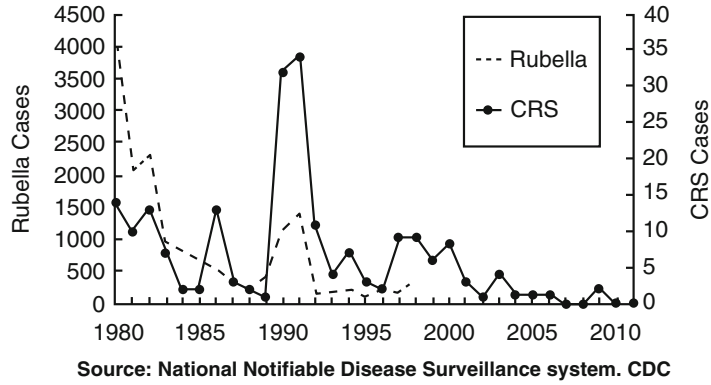

Fig. 5 Rubella cases in the USA, 1966–2009. Graph from CDC/vaccines/rubella

Measles virus is a single-stranded RNA virus member of the genus Morbilliform in the family *Paramyxoviridae*. Two membrane envelope proteins—fusion protein (F) and hemagglutinin (H)—are responsible for pathogenesis. There is only one antigenic type of measles virus. Measles is an airborne disease and is spread via respiratory transmission. The primary site of invasion and

replication is the respiratory epithelium. The incubation period is 10–12 days followed by a prodrome consisting of fever, cough, coryza, conjunctivitis, and Koplik spots—punctate bluish-white spots on red background on buccal mucosa which are pathognomonic of measles. The rash of measles is a maculopapular rash that develops 2–4 days after prodrome or 14 days after exposure and spreads from the head over the trunk to the extremities during a 3–4-day period. The rash fades over next 3–4 days in the order of its appearance. The complications of measles include diarrhea, otitis media, pneumonia, encephalitis, seizures, and rarely death. Diagnosis is clinical and is confirmed by serological testing—most commonly by ELISA.

Prior to 1963, approximately 500,000 cases and 500 deaths were reported annually in the USA [69], with epidemic cycles every 2–3 years. Following vaccine licensure in 1963, the incidence of measles decreased by more than 98 %. Between 1989 and 1991, there was a resurgence of measles with 55,622 cases in children less than 5 years of age with 123 reported deaths. Measles incidence then declined rapidly post-resurgence period owing to increased vaccination programs of preschool children, adolescents, and young adults. The Centers for Disease Control reported a total of 911 cases of measles from 2001 to 2011; however owing to vaccination delay and misguided ideas about vaccination, 159 cases have been reported in the USA in 2015, the greatest number of cases reported since measles elimination was documented since 2001.

In 1963, both a killed and a live attenuated Edmonston B strain of measles virus were licensed in the USA. The killed vaccine was withdrawn in 1967 owing to development of atypical measles. The Edmonston B strain was withdrawn in 1975 due to a high incidence of post-vaccination fever and rash. A live, further attenuated Schwarz strain was licensed in 1965, but is no longer used in the USA. The only available measles vaccine is a live, further attenuated Edmonston-Enders strain (Moraten). The vaccine is available combined with MMR, or combined with measles, mumps, rubella, and varicella as MMRV (ProQuad).

Mumps was first described by Hippocrates in the fifth century BC and scientifically detailed by Robert Hamilton, a British physician in 1790 [70]. In 1935, Johnson and Goodpasture [71] proved viral cause for this disease. Although mumps is a benign disease of childhood, it was a major cause of morbidity among soldiers during American Civil War and World Wars I and II [72–74].

Mumps virus, a *Paramyxovirus* with a single-stranded RNA genome, causes a communicable acute viral illness via airborne transmission or by direct contact with infected saliva. After acquisition, the virus replicates in the nasopharynx and regional lymph nodes. Viremia develops 12–25 days after exposure affecting the meninges and various glandular organs such as the salivary glands,

pancreas, testes, and ovaries. Prodromal symptoms include low-grade fever, myalgia, anorexia, and headache. Parotitis is the most common clinical finding occurring in 30–40 % of infected persons, although up to 20 % mumps infections are asymptomatic. Complications of mumps include aseptic meningitis, orchitis, oophoritis, pancreatitis, and rarely deafness and death. Laboratory diagnosis is made by using serology or PCR detection of the mumps virus. An estimated 212,000 cases of mumps occurred in the USA in 1964. After the licensure of the Jeryl Lynn Strain of attenuated mumps virus vaccine in 1967, the number of reported mumps cases has steadily declined except for sporadic resurgences.

The first mumps vaccine was developed in 1948 but it was withdrawn in mid-1950s owing to limited temporal immunity. All mumps vaccines currently in use contain live viruses. The various mumps vaccine strains available are Jeryl Lynn, Urabe AM9, Leningrad-Zagreb, and Leningrad-3. The currently used mumps vaccine in the USA is the Jeryl Lynn strain, a live attenuated mumps vaccine. It is available combined with measles and rubella as MMR, or combined with measles, rubella, and varicella vaccine as MMRV (ProQuad).

Rubella was initially described in the late eighteenth century and was differentiated from other exanthems by German physicians, hence the name German measles [75]. The term rubella, meaning "little red" [76], was coined by a British physician in 1841 during an outbreak in India. However it was only in 1941 that Norman McAlister Gregg [77], an Australian ophthalmologist, recognized congenital rubella syndrome (CRS). The rubella virus was first isolated by Parkman and Weller in 1962. The pandemic in Europe during 1962–1963 and in the USA in 1964–1965 spurred work on the rubella vaccine. The highest incidence of rubella in the USA was in 1969. The licensure of the vaccine that year led to a marked decrease in the incidence of rubella and CRS. A record low of seven cases was reported in 2003 and in the year 2004 rubella was no longer considered to be endemic in the USA, but it remains an ongoing problem in many parts of the developing world. On April 29, 2015, the World Health Organization declared the elimination of rubella in the Americas.

Rubella virus is an RNA virus belonging to *Togaviridae* family and genus *Rubivirus*. Rubella spreads by respiratory aerosols and primary replication occurs in the nasopharynx and regional lymph nodes. The incubation period is 14–21 days. The first week after exposure is usually symptom free followed by second week of viremia, low-grade fever, malaise, and lymphadenopathy. The characteristic maculopapular erythematous rash develops 14–17 days after exposure; it begins on the face and spreads downward. Other symptoms include arthralgia, arthritis, conjunctivitis, testalgia, or orchitis. The complications of rubella are chronic arthritis, thrombocytopenia purpura, encephalitis, orchitis, neuritis, and a rare late

syndrome of progressive panencephalitis. Congenital rubella syndrome affects 85 % of infants infected during first trimester but congenital defects are rare if infection occurs after the 20th week of gestation. The virus may affect all organs and cause congenital defects, the most common of which is deafness. Other prominent clinical findings include cataracts, glaucoma, retinopathy, patent ductus arteriosus, ventricular septal defect, pulmonic stenosis, coarctation of aorta, and neurologic and boney abnormalities. The laboratory diagnosis of rubella is made by isolation of the virus from clinical specimens or by serology using enzyme immunoassay.

In 1969, three rubella vaccines were licensed: HPV-77:DE5 (Meruva), HPV-77:DK-12 (Rubelogen), and GMK-3:RK53 (Cendevax). RA 27/3, a human diploid fibroblast strain (Meruvax-II, Merck), was licensed in 1979 and all other strains were discontinued. RA 27/3 rubella vaccine was first isolated from a rubella-infected aborted fetus in 1965. The virus was attenuated using human diploid fibroblasts. The vaccine is available combined with measles and mumps vaccines as MMR, or combined with measles, mumps, rubella, and varicella as MMRV (ProQuad).

MMR or MMRV vaccine is routinely recommended for all children 12 months of age or older [78]. The first dose of MMR should be given on or after first birthday and the second dose is given between ages 4 and 6. High schools and colleges in the USA and other countries frequently require students to have received two doses of vaccine at some point in their lives prior to matriculation. The adverse reactions include fever, rash, thrombocytopenia, arthritis/arthropathy, encephalopathy and rarely parotitis, or deafness. MMR vaccine is contraindicated in pregnancy, immunocompromised patients, during acute illness, or those with severe allergic reaction to vaccine components which include neomycin.

13 Pertussis Vaccines

Pertussis or whooping cough is an infectious disease caused by *Bordetella pertussis*, a gram-negative bacillus.

Before the introduction of the whole-cell vaccine, there were over 250,000 cases of whooping cough per year and 10,000 deaths worldwide. The incidence of pertussis declined significantly with the implementation of universal vaccination. Pertussis incidence has been gradually increasing since the early 1980s. A total of 28,000 cases were reported in 2014, the largest number since 1959. The reasons for the increase are not clear. A total of 27,550 pertussis cases and 27 pertussis-related deaths were reported in 2010. The increase in disease incidence in the USA has mostly been seen in older children and adults, likely reflecting waning

immunity conferred by the vaccine, decreasing natural immunity, as well as decreasing vaccination rates. The numbers may underestimate the reality as this disease is underdiagnosed in adults [79].

Bordetella pertussis is a small, fastidious aerobic gram-negative rod, requiring specialized medium for culture. It produces multiple antigenic and biologically active products including pertussis toxin, filamentous hemagglutinin, agglutinogens, adenylate cyclase, pertactin, and tracheal cytotoxin. These products are responsible for the clinical features of pertussis disease, and an immune response to one or more produces immunity following infection.

The clinical presentation varies slightly between children and adults. In general, whooping cough is divided into three phases: the catarrhal or prodromal stage, the paroxysmal stage, and the convalescent stage. During the catarrhal stage, children present with signs and symptoms of an upper respiratory tract infection such as rhinorrhea, conjunctivitis, occasional cough, and fever. This generally lasts from 1 to 2 weeks. The paroxysmal stage is characterized by repeated episodes of severe cough accompanied by fits of spasm and, at the end of the paroxysm, may be accompanied by the classic whooping sound produced when rapidly inspiring air against a closed glottis. With the force of the coughing, children will often cough mucous plugs and can be accompanied by post-tussive emesis. These attacks occur more frequently at night. The paroxysmal stage can last as long as 6 weeks. Lastly, symptoms begin to wane and patients move on to the convalescent phase. Pertussis in adults can have a more atypical presentation, often appearing as a chronic cough [80] with a less defined course than classically described in children.

Whole-cell pertussis vaccine is composed of a formalin-inactivated suspension of *B. pertussis* cells. It was developed in the 1930s and has been available in practice since the 1940s. Based on efficacy studies, the vaccine conferred 70–90 % efficacy in protecting from severe pertussis. Local reactions were common and occasionally would be accompanied by fever. This led to the creation of an acellular vaccine associated with less adverse effects. Whole-cell pertussis vaccine is no longer available in the USA but is still available elsewhere. Acellular vaccines are subunit vaccines that contain inactivated components of *Bordetella pertussis*. These are only available in combination with diphtheria and tetanus toxoid. Efficacy has ranged from 80 to 85 % [81]. The primary series of DTaP vaccines consists of four doses, the first three doses given at 4- to 8-week intervals (minimum of 4 weeks), and beginning at 6 weeks to 2 months of age. The fourth dose is given 6–12 months after the third to maintain adequate immunity for the ensuing preschool years [81].

14 Pneumococcal Vaccines

Pneumococcal infections which include pneumonia and invasive infections such as bacteremia and meningitis constitute a major source of morbidity and mortality both among the very young and the elderly, with a special impact in those populations unable to generate antibodies to the polysaccharide capsule of *Streptococcus pneumoniae*. The highest burden of invasive disease occurs in those with HIV, younger than 2 years and those older than 65 years, with the highest mortality occurring in those older than 65 [82].

It is estimated that before the introduction of the PCV-7 vaccine, this bacteria caused 17,000 cases of invasive disease per year including 700 cases of meningitis and 200 deaths in children younger than 5. In the USA, before the introduction of the pneumococcal conjugated vaccine there were an estimated 15 million office visits for acute otitis media resulting in 5 billion dollars annually.

Streptococcus pneumoniae causes a wide range of diseases, most commonly causing pneumonia and otitis media but also having the potential to cause invasive disease such as bacteremia and meningitis [82]. With the exception of the great apes, humans are the only organisms affected by Pneumococcus. It is carried in the nasopharynx from whence it can be readily transmitted via droplets. Carriage length varies by serotype and is usually asymptomatic but can result in acute disease such as otitis media or invasive disease. The organism's capsule is its most important virulence factor. It protects the bacteria against phagocytosis and complement activation and antibodies. It can also aid in adherence to epithelium.

Forty serogroups encompassing 93 serotypes have been described. Among these, a small proportion is responsible for the majority of invasive diseases with the ten most common ones being isolated in more than 80 % of cases in the USA. In studies done prior to the introduction of pneumococcal vaccines serotypes 14, 16b, 1, 23F, 5, and 19F in descending order were the most common. Distribution and causality have varied with the introduction of the vaccines with a trend to shift into different disease-causing strains not covered by currently available vaccines.

Currently, two types of pneumococcal vaccines are currently available. These are the 23 valent polysaccharide vaccines (PV23) and the 13 valent conjugated vaccine (PV13). They both contain purified capsular polysaccharide component of Pneumococcus. The 23 valent vaccine contains capsular materials from 23 serotypes that have historically been known to cause 85–90 % of invasive diseases. The serotypes included in this vaccine are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. This vaccine has been shown to be efficacious in decreasing the incidence of invasive disease (i.e., bacteremia and meningitis) and noninvasive pneumococcal pneumonia [83, 84].

The 13 valent conjugated contains 13 capsular saccharides from the most common strains covalently linked to a nontoxic protein that is similar to diphtheria toxin. This covalent linking renders the vaccine immunogenic in infants and toddlers. It has also been shown to have increased immunogenicity in immune-compromised individuals such as asplenic patients or patients with HIV. The serotypes included by this vaccine are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Several studies have demonstrated the efficacy of the conjugated pneumococcal vaccine [85, 86]. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97 %, and reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89 %. Children who received PCV7 had 7 % fewer episodes of acute otitis media and underwent 20 % fewer tympanostomy tube placements than did unvaccinated children.

The indications for both vaccines vary slightly with the conjugated vaccine being indicated in very specific groups of patients [86].

PPSV 23 alone should be given to:

- Cigarette smokers
- Alcoholics
- People with chronic heart disease excluding hypertension
- Chronic lung disease including asthmatics
- Diabetes mellitus
- Chronic liver disease

A combination of PSV 23 and the PVC13 should be given to:

- People older than 65
- Patients with cochlear implants
- Patients with CSF leak
- Functional or anatomical asplenia
- Congenital or acquired immune deficiency including HIV

The latter group of patients comprises those at greatest risk for invasive disease in whom increased immunogenicity has been demonstrated with conjugated 13 valent vaccine.

15 Rotavirus Vaccines

Rotavirus is the leading cause of acute gastroenteritis among infants and young children worldwide. *Rotavirus* is estimated to account for one-third of the estimated 1.3 million deaths yearly from diarrhea [87–89]. In the prevaccine era, rotavirus accounted for 2.7 million illness episodes and around $1 billion annually in medical costs in the USA [90, 91].

Rotaviruses are 70 nm double-stranded RNA icosahedral viruses belonging to the family *Reoviridae*. The virus is composed of an outer and inner capsid and a core. Three major structural proteins (VP 4, VP 6, VP 7) and one nonstructural protein (NSP4) are of interest in vaccine development. The exact mode of transmission of rotavirus is unknown. It is assumed to be spread from person to person contact or aerosolized respiratory droplets. Incubation period is short, usually less than 48 h. The virus replicates in the mature villous epithelial cells of the small intestine causing malabsorption. The nonstructural protein (NSP4) acts as an enterotoxin causing diarrhea [92]. Severe gastrointestinal illness by rotavirus mainly occurs in children 3–24 months [93, 94]. Infection during first month of life provides IgA-mediated protection against moderate-to-severe illness on reinfection. Rotaviral infection may be asymptomatic or cause self-limited diarrheal illness or result in severe dehydrating diarrhea complicated by electrolyte imbalances, metabolic acidosis, and multiorgan involvement. Diagnosis is made by detection of rotavirus antigen in stool by enzyme-linked immunosorbent assay.

The first rotavirus vaccine, RotaShield (RRV-TV, rhesus-based tetravalent rotavirus vaccine), was introduced in the USA in 1998 but was withdrawn from the market a year later because of its association with intussusception 3–14 days after administration of first dose of vaccine. Currently there are two rotavirus vaccines licensed in the USA—RV5 (RotaTeq) and RV1 (Rotarix). RotaTeq is a live oral vaccine licensed in 2006. It contains five reassortment rotaviruses developed from human and bovine rotavirus strains. The vaccine viruses are suspended in buffer solution. Rotarix is also a live oral vaccine, licensed in 2008. It contains one strain of live attenuated human rotavirus type G1P1A [8]. The vaccine is a lyophilized powder that is reconstituted before administration. Both these vaccines contain no preservatives or thimerosal. The vaccine effectiveness is 74–87 % against any rotavirus gastroenteritis and 85–98 % in severe rotavirus gastroenteritis. Both vaccines significantly reduce physician visits, hospitalization, and overall morbidity and mortality.

The ACIP recommends [95] routine vaccination of all infants, administered as a series of either two doses of RV1 or three doses of RV5 beginning at 2 months of age or as early as 6 weeks with subsequent doses in the series separated by 1–2 months. The maximum age for any dose is 8 months. The only contraindication to the vaccine is a severe allergic reaction to vaccine components, a history of intussusception, or severe combined immunodeficiency syndrome. The common side effects were vomiting, diarrhea, fever, and irritability and no serious reactions have been reported so far.

Rotavirus disease among infants and young children significantly decreased after the introduction of the vaccines. The vaccine prevents an estimated 50,000 hospitalizations among US infants

and indirectly protects older children and adults. The CDC uses the National Respiratory and Enteric Virus Surveillance System (NREVSS) to estimate burden of the disease and disease trend and evaluate the impact of vaccination in the USA.

16 Tetanus Toxoid

Tetanus is an acute and often fatal disease caused by an exotoxin produced by *Clostridium tetani*. It is unique among vaccine-preventable diseases in that it is not communicable. Records from antiquity contain descriptions of the disease but it was not until the late nineteenth century that the etiology of the disease was demonstrated by Carle and Rattone [96] by injecting the contents of a pustule in a human victim into the sciatic nerve of a rabbit, thus producing the symptoms of tetanus. Soil samples inoculated into rabbits would also cause disease as demonstrated by Nocolaier. In 1897, Nocard demonstrated the protective effect of passively transferred antitoxin, and passive immunization in humans was used for treatment and prophylaxis during World War I. The tetanus toxoid was first successfully synthesized in 1924.

Clostridium tetani is a slender gram-positive, anaerobic rod that can develop a distal spore giving it the semblance of a drumstick. The organism is sensitive to heat and cannot survive in the presence of oxygen. Its spores however are very resistant to heat and usual antiseptics. The spores are widely distributed in the soil and intestines of many animals. Manure-treated soils contain an abundance of spores. The organism produces two toxins, tetanolysin and tetanospasmin, of which the latter is the neurotoxin responsible for clinical disease.

Clostridium tetani usually enters the body through a wound. Although the incubation period varies, disease tends to occur within 3–21 days following spore inoculation. The site of inoculation seems to correlate with the incubation period duration. Under anaerobic conditions, the spores germinate and toxin production ensues. Toxin enters the bloodstream and lymphatics where it ultimately leads to the central nervous system and motor end plates where tetanus toxin interferes with neurotransmitter release (specifically GABA) blocking inhibitor impulses. This results in unopposed and uncontrollable muscle contraction and spasm [96].

In general, there are three forms of tetanus: localized, cephalic, and generalized. Localized tetanus is uncommon and is characterized by spastic muscle contractions at the site of initial inoculation [96]. These may persist for a week. Cephalic tetanus is a rare form of the disease usually following otitis media in which cranial nerves and facial muscles are affected. More than 80 % of cases are of generalized tetanus. This usually presents initially with trismus or lockjaw and risus sardonicus and progresses to generalized tetanus

spasm. Generalized tetanus is usually accompanied by respiratory failure caused by generalized spasticity of respiratory muscles. Before the availability of medications to counteract spams and assisted ventilation, respiratory failure was the most common cause of death with tetanus. Generalized tetanus can also result in generalized autonomic dysfunction resulting in blood pressure variations, tachycardia, bradycardia, flushing, and arrhythmias. The duration of most severe illness usually is from 1 to 4 weeks with mortality reported between 20 and 70 %.

Tetanus toxoid was first used in 1924 and was widely adopted in the armed forces during World War II. Tetanus toxoid consists of formaldehyde-treated toxin. There are two types of toxoid available, adsorbed and fluid toxoid [97]. Current preparations are available as combinations with either diphtheria and acellular pertussis or diphtheria toxoid alone. As with other inactivated vaccines and toxoids, more than one dose is required to confer immunity. After a series of three vaccines, essentially all recipients develop antitoxin levels considered protective. Effectiveness has never been objectively studied but it is inferred by antitoxin levels to be 100 % if given within the prior 10 years.

A decline in cases of tetanus was observed in the early twentieth century with a further rapid decline after tetanus toxoid was introduced. Mortality rates have also dropped significantly, demonstrated to be as low as 10 % in recent years [98]. Virtually all cases of tetanus reported have occurred in those who were never vaccinated or did not have booster vaccine in the prior 10 years.

17 Tuberculosis Vaccine

There is probably no vaccine in wide use that has been the subject of as much scrutiny and controversy as the tuberculosis vaccine commonly referred to as Bacillus Calmette-Guerin (BCG) [99]. It is one of the oldest vaccines available and has been widely adopted worldwide except for the USA and the Netherlands. The estimated efficacy rates have varied widely in different studies ranging from broad protection of more than 80 % to no efficacy at all.

Tuberculosis has caused disease in human for many millennia with cases being noted in mummies from the age of the Pharaohs in Egypt. It is likely responsible for the majority of deaths in the USA and Europe in recorded history. During the tenth century it was responsible for 400 in every 100,000 deaths. With improving living conditions, sanitation, and social advances came a decrease in the incidence and mortality in the industrialized world.

The disease is caused by the pathogen *Mycobacterium tuberculosis* first described by Koch in 1882. Tuberculosis is acquired through the respiratory tract and from there can enter a latent stage or progress to active disease. The majority of patients infected initially are asymptomatic, entering a latent stage where the

immune system keeps the disease in check. For most individuals infected with tuberculosis, the average lifetime risk of reactivation disease is roughly 10 %. Should disease become active, tuberculosis most commonly causes disease in the lungs but has the potential to disseminate to virtually any organ [99]. The time between primary infection and reactivation can span anywhere from weeks to years which is one of the more challenging aspects of conducting trials for a vaccine. It is a highly infectious disease with 25–50 % of close contacts becoming infected when exposed to an active case.

The live attenuated oral BCG vaccine was first given to infants in Paris in 1921 and has undergone substantial changes since then. The attenuated *Mycobacterium bovis* strain was first used by French scientists Calmette and Guerin where they studied a strain of *M. bovis* causing tuberculous mastitis in cows. They painstakingly cultured a strain every 3 weeks over the course of 13 years leading to a non-pathogenic and phenotypically different bacteria. BCG has been part of the expanded program for immunization of the WHO since the 1970s and has been administered some four billion times with relatively few significant side effects. Only recently has it been noted that administration of BCG can result in active infection in patients with advanced immune suppression such as those with HIV. Recommendations have changed as to not include such patients in current immunization schedules.

The extent of efficacy of this vaccine seems to depend on prior exposure to Mycobacteria which itself is a function of age. Trials on efficacy have widely varied with some trials demonstrating great protection against pulmonary tuberculosis and others showing virtually no protection at all [100]. In a meta-analysis performed in 2012, investigators found that in children who were school aged with negative prior tuberculin testing a relative risk of 0.26 was achieved and a relative risk of 0.41 was achieved in neonates. This effect seems to disappear in adolescent trials although some protection was observed in adult trials. Factors that may explain this decrease in protection during the teenage years include the fact that the immune system may not be mature enough when first administered to confer long-lasting immunity, and co-infection with certain helminthic and viral pathogens which could depress immunity (the extreme of this being HIV). The greatest efficacy of the tuberculous vaccine seems to be in decreasing disseminated disease and meningitis in children where protection can be as high as 80 % [101]. The effect of BCG on immunity seems to be greatest during the first 10–15 years after administration with no significant increased protection noted in adolescents and adults.

The BCG vaccine is currently administered to newborns in countries that have adopted the vaccine in the form of one intradermal injection. The dose of vaccine varies by age and formulation. The official WHO recommendation is to receive a single intradermal vaccine dose.

18 Yellow Fever Vaccine

Although taxonomic studies of the virus have indicated an African origin, yellow fever was first recognized during an outbreak in the Americas in 1648. The current consensus is that the virus was introduced into the new world through mosquito-infested slave trading vessels from West Africa. Epidemics affected the USA including the Philadelphia epidemic of 1793 that killed one-tenth of the city's population. Sanitary measures including the introduction of piped water inadvertently helped to diminish transmission of the disease. Advances in the early twentieth century, which included the identification of the vector, isolation of the virus, and development of a vaccine, all served to curtail the prevalence of this disease. However, more than 70 years after the development of an effective vaccine, areas of endemic transmission continue to exist with the periodic recurrence of outbreaks.

Yellow fever virus belongs to the genus *Flavivirus*. *Flaviviruses* are small spherical positive-sense single-stranded viruses with an envelope containing lipid and two envelope proteins, E and M. The genome of the prototype yellow fever virus strain 17D-204 contains 10,862 nucleotides, composed of a 5′-terminal type I cap structure, a short 5′ noncoding region, a single open reading frame of 10,233 nucleotides, and a 3′ noncoding region. The E protein exhibits important biologic properties including attachment to host cell receptors, endosomal membrane fusion, and display of sites mediating hemagglutination and viral neutralization.

Yellow fever ranges in severity from a nonspecific flu-like-type illness to a hemorrhagic fever that is fatal in 50 % of cases. A significant percentage of infections go undetected. The incubation period ranges from 3 to 6 days and is followed by the abrupt presentation of fever, headaches, and muscle aches accompanied by physical findings such as injected conjunctiva, facial flushing, and leukopenia. Most cases resolve after this phase, but some go on to develop, after being free of fever for hours or days, high fever, lumbosacral pain, headaches, abdominal pain, and somnolence. This is a severe multisystemic illness dominated by icteric hepatitis and hemorrhagic diathesis with prominent gastrointestinal bleeding, hematemesis, epistaxis, petechiae, and purpuric hemorrhages.

Yellow fever vaccine is a live-virus vaccine which has been used for several decades. A single dose protects against disease for 10 years or more. Infants, toddlers, pregnant women, and patients with HIV may not have as robust a response to the vaccine.

Adverse reactions to the yellow fever vaccine are very rare but in some instances can be severe. The more severe reactions are lumped into two syndromes known as viscerotropic adverse reactions and neurotropic adverse reactions [102]. The vaccine is contraindicated in those with allergy to the vaccine components, age less than 6 months, symptomatic HIV infection or CD4 count

less than 200, thymic disorder-associated immune dysfunction, and other immunosuppressive diseases and therapies.

Yellow fever vaccine is recommended for persons aged ≥9 months that are traveling to or living in areas at risk for yellow fever virus transmission in South America and Africa. A single dose given every 10 years is considered effective for people who are traveling to areas of high endemicity. Certain countries require record of immunization before entry is allowed including proof of vaccination by documentation on an "International Certificate of Vaccination or Prophylaxis" for yellow fever.

19 Zoster Vaccine

The *varicella zoster virus (VZV)* belongs to the family of *Alfa herpes viruses* who have the ability to maintain a latent infection in the sensory ganglia during primary infection. The virus initially presents as a diffuse vesicular eruption, varicella (chickenpox) which is a prevalent and widespread affliction worldwide. Thoracic and cervical ganglia contain VZV detectable by PCR in as many as 90 % of adults. It is from these ganglia that herpes zoster subsequently arises.

Although the mechanism by which latency is maintained is not fully understood, the evidence points at the importance of the host-specific immune response which first develops soon after the appearance of skin lesions in varicella. These responses include the development of a polyclonal anti-VZV) antibody and T-cell-mediated responses. These persist lifelong and prevent the appearance of new episodes of varicella.

With increasing age and T-cell immune suppression, the risk of developing herpes zoster increases. The CDC estimates that 1 in 3 Americans will develop herpes zoster in their lifetime. About half of the cases occur in men and women older than 60 and there are approximately 1 million new cases per year. Herpes zoster is a dermatologic vesicular disease which affects a particular dermatome in individuals as a consequence of the reactivation of the *VZV.*) The disease is characterized by a prodromal stage where pain predominates, followed by the classic appearance of a vesicular rash following the trajectory of the affected dermatome. The most severe consequence of zoster is the appearance of postherpetic neuralgia which can result in significant pain and disability in those affected by it. Zoster vaccination seeks to curtail the risk of herpes zoster and the development of postherpetic neuralgia [103].

The currently available vaccine is a live attenuated form of the virus called the Oka strain of VZV. It is essentially the same vaccine given for varicella but with 14 times the potency. It was first licensed in the USA in 2006. It is also licensed in the EU and Canada. It is currently recommended for patients 60 years of age or older

with the purpose of preventing the development of herpes zoster and postherpetic neuralgia.

Regarding efficacy, a large trial conducted between 1999 and 2004 involving thousands of patients demonstrated that the vaccine was effective in reducing the risk of disease by 51 % and the risk of postherpetic neuralgia by 67 %. Studies in younger cohorts of patients have shown similar results and this led the EU to approve the use of the zoster vaccine in patients between ages 50 and 59 [104]. In the USA the FDA has approved the vaccine beginning at age 50; however the ACIP recommends that the vaccine not be given until age 60.

Given the vaccine is an attenuated virus, it is contraindicated in those with significant immune suppression such as patients with advanced HIV, those receiving corticosteroids or other immune suppressant medication, or those with active malignancies receiving chemotherapy. Overall the safety profile for this vaccine is excellent with most patients reporting no side effects.

Current recommendation is to give one intramuscular dose in patients older than 60 years. Given this is a live vaccine, it should not be administered to patients with significant immune suppression.

20 HIV Vaccine

Since the beginning of the epidemic in the early 1980s, the natural history of HIV infection has evolved from one of certain death to a treatable chronic condition. Currently, there are about 35 million people living with HIV and the disease was responsible for 1.5 million deaths in 2013. In the USA there are approximately 1.2 million living with HIV of which 14 % are unaware of their diagnosis. Roughly 50,000 people develop new infections annually in the USA alone.

The two agents that cause AIDS are *human immunodeficiency 1 (HIV-1) and HIV-2*. These viruses are *Lentiviruses* that belong to the family *Retroviridae*. These are enveloped RNA viruses that cause slowly progressive infections which produce clinical disease after a prolonged latency. In untreated patients the subacute phase preceding clinical disease averages around 10 years. These viruses depend on, and possess, the enzyme reverse transcriptase which transforms viral RNA into proviral DNA. HIV targets CD4 cells, a central component of the immune system, and enters them by interacting with the surface coreceptors CCR5 and CXCR4. Infection leads to a steady decline of CD4 cells eventually leading to the development of AIDS in those untreated.

Current antiretroviral medications are very effective at bringing HIV under control and can result in a near-normal life-span. While public health measures have significantly decreased the incidence of new infections, it is clear that a vaccine would be the only effective

way of controlling the epidemic. There have been many obstacles to the development of an effective HIV vaccine. Chief among these is the fact that there is no documented case of a human spontaneously clearing the virus. Other important factors include the antigenic diversity and hypervariability of the virus, its ability to rapidly generate escape mutants, and the lack of an ideal animal model.

Over the last 30 years, only four vaccine concepts have been evaluated in clinical efficacy trials. These include the use of purified HIV-1 envelope proteins, recombinant adenovirus and poxvirus vectors, and plasmid DNA vaccines. While there have been several phase I and phase II trials evaluating safety and immunogenicity of proposed HIV vaccines, to date, there have only been a handful of Phase III trials that have evaluated the efficacy of HIV vaccines. Of those, only one showed a statistically significant result. Known as the "Thai trial," RV144 was a randomized placebo-controlled trial looking at the use of a *Canarypox* vector vaccine expressing gp120 clad E GAG and protease from clade B boosted by AIDSVAX (rGP protein 120 from 2 clade B). Looking at a population of around 16,000 low-risk individuals, in the modified intention-to-treat analysis, this vaccination strategy demonstrated a 31 % reduction in disease acquisition [105]. While the results are modest, it serves as a proof of concept that producing an effective vaccine against HIV is in fact possible.

An exciting field of study in which much of the current study for HIV vaccine is focused is the concept of broadly neutralizing antibodies. These are antibodies that target the conserved regions of HIV-1 Env. Although a subset of patients develop broadly neutralizing antibodies after years of infection, only a small percentage produce antibodies that are potent as well as broad. No vaccine to date has been able to elicit a broadly neutralizing antibody response. The use of passive immunization using broadly neutralizing antibodies remains an attractive but challenging proposal [106].

The landscape for the development of an effective HIV vaccine is one that should generate optimism amongst physicians and patients. The results of the RV-144 trial have generated follow-up studies that are currently under way [107]. This along with the advances in understanding of broadly neutralizing antibodies should be viewed as a great stride in the search for an effective vaccine

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