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Successful Vaccines

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Abstract

Vaccines are considered one of the most important advances in modern medicine and have greatly improved our quality of life by reducing or eliminating many serious infectious diseases. Successful vaccines have been developed against many of the most common human pathogens and this success has not been dependent upon any one specific class of vaccine since subunit vaccines, non-replicating whole-virus or whole-bacteria vaccines, and attenuated live vaccines have all been effective for particular vaccine targets. After completing the initial vaccination series, one common aspect of successful vaccines is that they induce long-term protective immunity. In contrast, several partially successful vaccines appear to induce protection that is relatively short-lived and it is likely that long-term protective immunity will be critical for making effective vaccines against our most challenging diseases such as AIDS and malaria.

1. Introduction

The effect of vaccines on public health is truly remarkable. One study examining the impact of childhood vaccination on the 2001 US birth cohort found that vaccines prevented 33,000 deaths and 14 million cases of disease (Zhou et al. 2005). Among 73 nations supported by the GAVI alliance, mathematical models project that vaccines will prevent 23.3 million deaths from 2011–2020 compared to what would have occurred if there were no vaccines available (Lee et al. 2013). Vaccines have been developed against a wide assortment of human pathogens (Table 1). There are vaccines against bacterial toxins (e.g., tetanus and diphtheria toxins), acute viral pathogens (e.g., measles, mumps, rubella), latent or chronic viral pathogens (e.g., varicella zoster virus [VZV] and human papilloma virus [HPV], respectively), respiratory pathogens (e.g., influenza, *Bordetella pertussis*), and enteric pathogens (e.g., poliovirus, *Salmonella typhi*). Most licensed vaccines can be categorized as (a) live, attenuated vaccines, (b) non-replicating whole-particle vaccines (including virus-like particles, or VLPs), and (c) subunit vaccines. There are similar numbers of licensed vaccines in each of these categories (Table 1) and this illustrates the point that no single vaccine approach is superior to another, but instead the approach varies according to each individual pathogen and the feasibility, safety, and efficacy required to develop a successful

vaccine to that particular pathogen. Interestingly, influenza represents the only example in which there is at least one licensed vaccine listed in each of these three categories.

2. Successes and failures of live attenuated vaccines

There are currently 13 diseases for which live, attenuated vaccines have been developed and licensed for commercial use (Table 1). Development of successful vaccines is typically easier when there is (a) a single serotype, (b) the pathogen is antigenically stable, (c) diagnostic tests/clinical criteria for measuring disease burden are available, and (d) the vaccine is both safe and effective. Smallpox vaccination with vaccinia virus is the most famous example of a highly effective vaccine and at the time when people were faced with smallpox outbreaks, this vaccine was associated with each of these characteristics that led to the implementation of a successful vaccine. The smallpox vaccine is not only the first vaccine ever developed (Jenner 1798, 1799, 1800), but since Variola virus (the causative agent of smallpox) no longer exists in nature, this also represents the first example in which a vaccine was purposefully used to drive a species to extinction. Some of the best examples of successful live, attenuated vaccines include those developed against measles, mumps, and rubella (MMR). In contrast, other live, attenuated vaccines such as the oral polio vaccine (OPV) and the first licensed vaccine against rotavirus (RotaShield®) serve as important reminders that vaccines must be safe if they are going to be used successfully for routine vaccination.

2.1 Measles, Mumps, Rubella

One of the most common live attenuated vaccines in use today is the MMR vaccine. Although originally designed as three separate vaccines, attenuated strains of measles, mumps, and rubella were successfully formulated into a single combination vaccine in the US in 1971 (Strebel et al. 2013) and it continues to be used to provide protective immunity against pathogens responsible for what were once considered common childhood diseases. Similar to smallpox vaccination, they were developed against viruses that are antigenically stable and have only a single serotype. Even when combined with live, attenuated VZV to provide a quadrivalent vaccine, seroconversion rates remain high (measles; 97.1%, mumps; 96.0%, rubella; 98.8% and varicella; 93.5%, respectively) (Lieberman et al. 2006). Other vaccines against antigenically variable viruses (e.g., influenza) or pathogens with multiple serotypes (e.g., HPV) indicate that as vaccine technologies have improved and evolved, there are opportunities to combat more complicated and challenging pathogens through effective immunization programs. Although nearly all vaccines require at least one booster dose in order to maintain long-term protective immunity (Slifka and Amanna 2014), many of our most successful vaccines have achieved the appropriate balance of both safety and efficacy.

2.2 Rotavirus and Poliovirus

There are many aspects to a vaccine that are required for them to be considered successful and one of the most important parameters for routine vaccines is patient safety. When vaccines demonstrate safety and efficacy during Phase II/III trials, then they have the opportunity to be licensed for commercial production while continuing to be monitored post-licensure (i.e., Phase IV). The RotaShield vaccine developed against rotavirus

represents a vaccine that failed post-licensure due to an unacceptably high rate of reactogenicity in which serious adverse events (e.g., intussusception) reached 90–214 cases per million administered doses (Kramarz et al. 2001; Murphy et al. 2001). Following licensure in 1998, it was subsequently pulled from the market by the end of 1999. Live, attenuated rotavirus vaccines with improved safety profiles (Rotarix® and RotaTeq®) have now entered the market to address this important clinical need. Similarly, live OPV provided good immunogenicity and protective efficacy, but also caused vaccine-associated paralytic poliomyelitis (VAPP) at a rate of 0.4–0.5 cases per million administered doses (Prevots et al. 1994; Hao et al. 2008). Because of its widespread use in the US, this resulted in an average of 9 children each year from 1961–1989 who suffered paralysis due to OPV (Alexander et al. 2004). Since polio was no longer endemic in the US, the OPV vaccine was causing more cases of paralysis than the wild-type polioviruses that it was designed to prevent. In 2000, the OPV vaccine regimen was abandoned in favor of the safer inactivated polio vaccine (IPV) series and VAPP has been eliminated (Alexander et al. 2004).

3. Successes and failures of non-replicating/inactivated vaccines

Successful non-replicating/inactivated vaccines have been licensed for 11 different pathogens and include both viruses and bacteria (Table 1). As described below, the hepatitis A virus (HAV) vaccine represents a striking success for whole-virion inactivated vaccines, with exceptional efficacy and long-term antibody persistence demonstrated for up to 20 years post-vaccination (Theeten et al. 2015). The HPV vaccine utilizes advanced VLP technology and is able to protect against chronic viral infection, prevent HPV-associated cancers, and potentially induce life-long immunity with as few as two doses or even a single immunization (Safaeian et al. 2013; Kreimer et al. 2015). In contrast to these success stories, unsuccessful attempts to develop formaldehyde-inactivated measles and respiratory syncytial virus (RSV) vaccines in the 1960s indicate that an inactivated whole-virus vaccine approach is not foolproof and several factors may have contributed to those failures (Polack 2007).

3.1 Hepatitis A

Infection with HAV was once a leading cause of viral hepatitis in the US, with 20,000–60,000 cases reported annually and fatality rates as high as 1.8% in adults >50 years of age (Centers for Disease Control and Prevention 2015c). Vaccine development against HAV benefited from several key factors including early studies demonstrating the efficacy of passive immunotherapy (Gellis et al. 1945; Havens and Paul 1945; Stokes and Neefe 1945; Hsia et al. 1954), the discovery of cell culture conditions for the propagation of HAV (Provost and Hilleman 1979), and passive and active immunization studies in appropriate animal models including chimpanzees and marmosets (Purcell et al. 1992; Provost et al. 1986). These critical elements supported the eventual development and licensure of two inactivated whole-virion, alum-adjuvanted vaccines (Havrix® and Vaqta®) in the US and since their implementation in the 1990s, the rates of disease have declined by >90% (Centers for Disease Control and Prevention 2015c). Efficacy for both vaccines is high, with estimates ranging from 94–100% (Wertzberger et al. 1992; Innis et al. 1994). HAV-specific antibodies have been identified as the key correlate of protective immunity following vaccination, and although an absolute lower limit has not been defined, titers >10–20

mIU/mL are generally considered protective (Centers for Disease Control and Prevention 1996).

One of the most impressive aspects of the inactivated HAV vaccines has been the durability of vaccine-induced antibody responses. Preliminary studies examining HAV-specific antibody titers demonstrated a rapid drop shortly after vaccination, but also showed a second, slower rate of decay, with protective immunity estimated to be maintained for 20–30 years following vaccination (Van Damme et al. 1994). Longer-term studies have confirmed and extended these initial results (Wiedermann et al. 1997; Rendi-Wagner et al. 2007; Theeten et al. 2015). In one notable study, antibody titers in subjects who received 2 doses of inactivated HAV vaccine were followed annually for up to 20 years post-vaccination (Theeten et al. 2015). Based on these results, it was estimated that at 40 years post-vaccination, 90% of vaccinees would maintain antibodies above the putative protective threshold. This may actually be an underestimate since, as noted by the authors, antibody decline appeared to level off over time with minimal changes to average group antibody titers from 11–20 years post-vaccination (Theeten et al. 2015). Remarkably, this data indicates that two doses of an alum-adsorbed inactivated vaccine may be sufficient to induce life-long immunity for most vaccine recipients.

3.2 Human Papilloma Virus

Exposure to HPV, typically transmitted at mucosal surfaces through sexual contact, can lead to persistent infection and a range of cancers (Centers for Disease Control and Prevention 2015d). Cervical cancer, caused almost exclusively by HPV, still bears a substantial burden on the US, with 4,074 deaths reported in 2012 alone (the most recent year with available data (Centers for Disease Control and Prevention 2015a)). Although more than 120 HPV types have been identified, a smaller subset of approximately 13–14 types are considered high-risk for developing cancer (Centers for Disease Control and Prevention 2015d). Successful development of HPV vaccines was precipitated by the discovery that the L1 capsid protein of the virus could self-assemble into VLPs and induce high-titer neutralizing antibodies (Kirnbauer et al. 1992). Papillomaviruses are species-restricted and this constrains the ability to assess HPV vaccine candidates directly in animals. However, several species-specific models (including mucosal challenge routes) were tested using L1 VLP candidates (Schiller and Lowy 1996). These animal studies demonstrated several key findings including (a) VLPs could protect prophylactically against disease but had no impact on established infections, (b) denatured VLPs were unable to elicit protective responses, suggesting that the three-dimensional conformation of the VLP was important to eliciting appropriate immunity, and (c) passively transferred antibodies from immunized animals were sufficient to protect against disease (Schiller and Lowy 1996).

These early animal studies of the L1 VLP approach were encouraging enough to prompt the NIH and several pharmaceutical companies to begin testing vaccine candidates in clinical studies (Schiller and Hidesheim 2000) that eventually led to key Phase III clinical trials with efficacy estimates ranging from 90–98% (Paavonen et al. 2007; The FUTURE II Study Group 2007). US licensure was granted by 2006 (quadrivalent Gardasil®) and 2009 (bivalent Cervarix®), with a 9-valent vaccine formulation (Gardasil 9®) licensed in 2014

(Centers for Disease Control and Prevention 2015d). Besides the number of HPV serotypes included in each formulation, the primary difference between the two vaccines is the inclusion of the monophosphoryl lipid A (MPL) adjuvant to the Cervarix vaccine in an effort to enhance antibody responses. In addition to providing impressive levels of protective efficacy, antibody responses to both vaccines appear to be long-lived. In one study, subjects vaccinated with 3-doses of either Cervarix or Gardasil were followed for up to 4 years (Einstein et al. 2014). While Cervarix induced higher serum and cervicovaginal neutralizing antibody titers, the rate of antibody decline was similar for both vaccines, with titers typically plateauing at 2–3 years and appearing stable thereafter (Einstein et al. 2014). Similar antibody kinetics have been observed by others (Giannini et al. 2006), with studies demonstrating both long-term antibody persistence (Safaeian et al. 2013) and efficacy following a single VLP vaccination (Kreimer et al. 2015). Although the precise mechanism of protection is unclear (Centers for Disease Control and Prevention 2015d), it is believed that serum neutralizing antibodies elicited by HPV vaccines can reach the genital tract through antibody exudation or transudation and thereby protect against infection at the mucosal surface (Schwarz and Leo 2008). Further evidence supporting this position comes from a recent study using a mouse cervicovaginal model which demonstrated that passive systemic transfer of immune serum alone could block HPV infection at the vaginal epithelium (Day et al. 2010). Unfortunately, despite proven efficacy, safety and durability of immunity, only 57% of adolescent girls and 35% of adolescent boys in the US had received a single HPV vaccine dose in 2013 (Stokley et al. 2014). This represents a significant missed opportunity, leaving a substantial number of young people at continued risk for infection and HPV-associated cancers.

3.3 Inactivated Measles and Respiratory Syncytial Virus Vaccines

The measles virus is one of the oldest recorded human pathogens, and despite the availability of an effective live attenuated vaccine, it remains a significant threat for many parts of the world (World Health Organization 2014). The first live vaccine was licensed in the US in 1963 and since that time the incidence of disease has dropped dramatically (Centers for Disease Control and Prevention 2015e). In addition to the live vaccine, a formaldehyde inactivated measles vaccine (FIMV) was also introduced in 1963 (Centers for Disease Control and Prevention 2015e). One trial involving over 5,000 children indicated the FIMV could induce seroconversion, though immunity appeared to wane rapidly with titers declining to undetectable levels within 6 months following vaccination (Carter et al. 1962). Efficacy studies reinforced this result, with a reasonably high efficacy of 81% observed during the first three months post-vaccination, but dropping to only 63% by 11–13 months (Guinee et al. 1966). More concerning however, were multiple reports detailing an unusual and severe form of measles following wild-type exposure of children, all having previously received the inactivated vaccine (Fulginiti et al. 1967; Rauh and Schmidt 1965). This condition, termed atypical measles, presented a range of symptoms including high rates of muscle and abdominal pain as well as peripheral edema and pneumonia (Fulginiti et al. 1967; Rauh and Schmidt 1965). Based on this and other reports, the vaccine was removed from the market by 1967, just 4 years after its initial licensure (Centers for Disease Control and Prevention 2015e).

RSV was first described in the 1950s, and was soon recognized as having a substantial impact on childhood respiratory health (Chanock et al. 1961; Beem et al. 1960). RSV remains a significant cause of acute lower respiratory infections among children <5 years of age, with a recent meta-analysis estimating an annual global burden of 33.8 million RSV-associated respiratory episodes and 66,000–199,000 deaths (Nair et al. 2010). Even in the US, an estimated 2.1 million children require medical attention each year due to RSV, with ~57,000 hospitalizations (Hall et al. 2009). Soon after the discovery of RSV, a formaldehyde-inactivated RSV (FIRSV) vaccine candidate was developed. However, multiple field efficacy trials demonstrated no protective immunity, and instead provided evidence for increased risk for enhanced RSV disease in vaccine recipients (Kapikian et al. 1969; Kim et al. 1969; Fulginiti et al. 1969; Chin et al. 1969). For example, children vaccinated with either the FIRSV candidate or an inactivated parainfluenza vaccine as a control, demonstrated RSV attack rates that were similar between these groups (65% and 53%, respectively). However, the hospitalization rates among infected children in the FIRSV cohort reached 80% (compared to a rate of only 5% in the control group) and the vaccine was associated with 2 deaths (Kim et al. 1969).

The similarities between the failed measles virus and RSV inactivated vaccines are evident (Polack 2007). Both pathogens are respiratory infections belonging to the *Paramyxoviridae* family and while the underlying mechanism of immune enhancement of disease remains unclear, it is believed that inactivated vaccines against either virus fail to induce protective high-avidity antibody, with skewing towards a Th2 response and subsequent enhanced inflammation following wild-type infection (Polack 2007; Acosta et al. 2016). Importantly, it is also clear that neutralizing antibodies are key to controlling either disease. Passive immunotherapy for the prevention of measles was described as early as 1924 (Zingher 1924), with recent meta-analysis confirming its value (Young et al. 2014). Similarly, prophylactic administration of a RSV neutralizing monoclonal antibody (palivizumab) has been shown to improve clinical outcomes and reduce hospitalizations in high-risk infants across multiple trials (Feltz et al. 2003; Pedraz et al. 2003; The IMPact RSV Study Group 1998). These results suggest that protective immunity through vaccination is achievable for both pathogens, and this has been accomplished for measles through the use of a live attenuated vaccine for >50 years. In contrast, while several new RSV vaccine candidates are under development, none have reached licensure (Jaberolansar et al. 2016). Nevertheless, recent positive results with a recombinant RSV F protein vaccine candidate in women (Glenn et al. 2016) provides some encouragement that the field is moving forward.

4. Successes and failures of subunit vaccines

Subunit vaccines have been licensed for 9 pathogens and encompass a range of approaches including purified toxoids, recombinant proteins, and either free or protein-conjugated polysaccharides (Table 1). In this section, we highlight the historic successes achieved with tetanus and diphtheria toxoids, both of which were developed in the 1920s (Roper et al. 2013; Tiwari and Wharton 2013). As a more recent example, we explore the development and implementation of successful vaccines against *Haemophilus influenza* type B (Hib) (Briere et al. 2014). These three examples have all benefited from having a defined antigen target with mechanisms of immunity established through passive immunization studies in

animal models as well as human clinical practice. By comparison, the development of acellular pertussis (aP) vaccines face ongoing challenges due to the waning immunity associated with this subunit vaccine approach (Plotkin 2014).

4.1 Tetanus and Diphtheria

Tetanus and diphtheria are both toxin-mediated diseases, against which effective vaccines have been widely available in the US for >70 years (Roper et al. 2013; Tiwari and Wharton 2013). Tetanus is mediated by the neurotoxin tetanospasmin (i.e., tetanus toxin) expressed by the bacterium, *Clostridium tetani* (Roper et al. 2013), and diphtheria results from the diphtheria toxin produced by *Corynebacterium diphtheriae* (Tiwari and Wharton 2013). Both vaccines consist of formaldehyde-inactivated toxoids with the diphtheria toxoid developed in 1920 (Tiwari and Wharton 2013) and the tetanus toxoid first described in 1924 (Roper et al. 2013). Efficacy of both toxoid vaccines has been demonstrated in large part by following epidemiology trends over time. Prior to broad introduction of the tetanus vaccine in the 1940s, the US recorded ~500–600 cases of tetanus annually (Centers for Disease Control and Prevention 2015f). In the post-vaccination era, this rate has dropped to ~30 cases annually and from 2001 – 2008 the CDC reported that in instances where vaccination status was reported, 41% of patients had never received a tetanus toxoid-containing vaccine (Centers for Disease Control and Prevention 2015f). Control of diphtheria (a communicable disease, in contrast to tetanus) has shown an even more dramatic impact. In the 1920s, there were an estimated 100,000–200,000 annual cases of diphtheria in the US with up to 15,000 deaths (Centers for Disease Control and Prevention 2015b). These rates dropped rapidly after introduction of the diphtheria vaccine, with no cases reported over an 11-year period from 2003–2013 (Adams et al. 2015). Immunity for both diseases is achieved through antibody-mediated toxin neutralization. For tetanus, immunity is considered 100% effective in preventing death if pre-existing antibody levels are above a putative protective threshold of 0.01 IU/mL (Amanna et al. 2008). This protective threshold is bolstered both by direct human challenge studies performed in the 1940s (Wolters and Dehmel 1942) as well as analysis of patients admitted with clinical signs of tetanus, wherein only those patients with titers <0.01 IU/mL experience the most severe symptoms or die from the disease (Goulon et al. 1972). For diphtheria, a minimal protective serum titer has also been defined as 0.01 IU/mL (Tiwari and Wharton 2013; Bjorkholm et al. 1986),

The success of the tetanus and diphtheria subunit vaccines may be viewed as a combination of several factors. Research into both toxins benefited from the development of relevant animal models and the demonstration that passive immunotherapy, directed against either toxin, was sufficient to achieve protective immunity (von Behring and Kitasato 1890). These results presented clear targets for vaccination with known mechanisms of protection (i.e., neutralizing antibodies). Furthermore, protection against both diseases can be achieved with relatively low levels of toxin-specific antibodies compared to the high levels of antibodies elicited through current vaccination schedules. For instance, following the completion of the primary tetanus and diphtheria vaccination series currently recommended in the US (consisting of 5 doses through 4–6 years of age) average anti-tetanus and anti-diphtheria antibody titers reach >7 IU/mL (Black et al. 2006), several orders of magnitude above their protective thresholds of 0.01 IU/mL. In terms of longevity, we and others have shown that

while antibody titers decline rapidly during the first few years following vaccination (typically 1–3 years following immunization (Amanna and Slifka 2010; Embree et al. 2015)), anti-toxin antibodies then display longer-lived single-order kinetics, with tetanus-specific antibody half-lives ranging from 11 to 14 years (Amanna et al. 2007; Hammarlund et al. 2016; Bonsignori et al. 2009), and diphtheria-specific titers declining with an estimated half-life of 19 to 27 years (Amanna et al. 2007; Hammarlund et al. 2016). While these rates of decline are somewhat faster compared to other vaccine and viral antigens (Amanna et al. 2007), based on current antibody levels measured among US adults, at least 95% of the population will remain protected against both tetanus and diphtheria for 30 years or more without requiring further booster vaccination (Hammarlund et al. 2016). In light of these results, the current US recommendation for adult tetanus/diphtheria booster doses to be administered every 10 years (Kim et al. 2016) should be reconsidered.

4.2 Haemophilus Influenza Type B

Hib is a gram-negative bacterium that was once the leading cause of bacterial meningitis in US children (Briere et al. 2014). In the pre-vaccine era, annual US rates of invasive Hib in children <5 years old averaged ~20 cases per 100,000, but this has dropped dramatically to an average incidence of ~0.15 per 100,000 following licensure of effective vaccines in the late 1980s (Briere et al. 2014). Early passive immunotherapy studies in humans indicated antibodies could play an important role in controlling disease (Beck and Janney 1947), and these results were confirmed in later studies of at-risk children prophylactically treated with hyperimmune globulin (Santosham et al. 1990). Hib anti-capsular antibody was identified as the mechanism of protection as early as 1944 using a passive immunity mouse protection model (Alexander et al. 1944) and these studies were cited as a key motivation for the initial development and clinical testing of several capsular polysaccharide vaccine candidates (Schneerson et al. 1971; Anderson et al. 1972). This history demonstrates that, as with tetanus and diphtheria, vaccine development for Hib benefited from a clear antigen target for antibody-mediated protection and was an approach supported by passive immunity proof-of-principle studies carried out in both animals and humans.

The first Hib polysaccharide vaccine was licensed for use in the US in 1985 (Briere et al. 2014). Pre-licensure studies had estimated VE of 90% (95% CI 58–99%) in 18–71 month old children, but also demonstrated low antibody responses and no efficacy in children <18 months old (Peltola et al. 1984; Ward et al. 1988). Post-licensure evaluation through several case-control studies suggested more modest VE of only 50% in children 18 months of age (Ward et al. 1988). Immunogenicity was greatly enhanced with the development of polysaccharide-protein conjugate vaccines, with several formulations licensed for use in children as young as 2 months old by 1990 (Briere et al. 2014). Numerous controlled trials estimated the efficacy of the conjugate vaccines at ~90% (Heath 1998), results which have been substantiated by the dramatic decrease of invasive Hib across multiple countries following widespread vaccination (Briere et al. 2014; Heath 1998). Current US recommendations suggest children should receive a 2–3 dose primary vaccination series (depending on the manufacturer) with a final booster dose typically given between 12–15 months of age (Briere et al. 2014). Following a similar vaccination schedule in UK infants, 98% of children were found to maintain Hib capsular polysaccharide antibody titers above

the putative protective threshold (defined as 0.15 µg/mL (Anderson 1984)) for up to 2 years following the final booster vaccination (Borrow et al. 2010). A similar study in Spain indicated no drop in geometric mean antibody concentrations from 4.5 to 5.5 years following the final booster vaccination, with >97% of children maintaining antibody concentrations above the 0.15 µg/mL threshold (Tejedor et al. 2012). In total, these results indicate that the Hib conjugate vaccine can induce long-term antibody responses and effectively control this invasive and life-threatening disease.

4.3 *Bordetella pertussis*

Bordetella pertussis, the bacterial pathogen responsible for the disease commonly known as whooping cough, was at one time a leading cause of childhood morbidity and mortality in the US (Morse 1913). In the decade just prior to vaccine licensure (1932–1941), annual reported attack rates averaged 157 per 100,000 persons, though the true rate has been estimated to be as high as 872 per 100,000 (Cherry 1999). Following the implementation of a whole-cell inactivated vaccine in the 1940s, disease burden dropped dramatically to a low of 0.5 cases per 100,000 persons by 1976 (Faulkner et al. 2015). While the positive public health impact of the whole-cell pertussis (wP) vaccine was striking, with estimates of VE ranging from 70–90% (Advisory Committee on Immunization Practices 1997), the vaccine elicited a relatively high rate of local and systemic adverse events (Cody et al. 1981). The most concerning adverse event was a potential link between vaccination and permanent brain damage due to encephalopathy (Walton et al. 2015; Shorvon and Berg 2008; Allen 2013). However, several of the reported case studies supporting this hypothesis have since been rediagnosed as Dravet syndrome, a form of epilepsy associated with specific genetic mutations (Reyes et al. 2011; Berkovic et al. 2006), and reappraisal of earlier studies calls into question whether any link between wP vaccination and encephalopathy truly exists (Shorvon and Berg 2008; Allen 2013).

Nevertheless, given the public concern surrounding the safety of the wP vaccine, several replacement subunit aP candidates were developed. Unlike tetanus, diphtheria, and Hib, one of the major limitations with the development of subunit vaccines for pertussis was the lack of a defined correlate of immunity against a specific *B. pertussis* component for vaccine-induced immunity. Early studies indicated a strong correlation between high serum agglutinin titers and protection from disease (Sako 1947; Medical Research Council 1956), but agglutinogens have been reported to include multiple targets such as pertactin (PRN), fimbriae-2 and 3 (FIM-2 and FIM-3), and lipooligosaccharide (LOS) (Cherry et al. 1998). Passive immunity studies performed in a mouse aerosol challenge model demonstrated that monoclonal antibodies against the pertussis toxin (PT), filamentous hemagglutinin (FHA) and FIM-2 could each protect mice against disease (Sato and Sato 1990), underscoring the complexity of the problem. Clinical results from early efficacy trials of aP vaccine candidates were likewise complex, suggesting that combinations of pre-existing antibody titers to a range of antigens, including PT, PRN and FIM-2, could be correlated with vaccine efficacy (Cherry et al. 1998; Storsaeter et al. 1998), but antibodies to FHA appeared to play no role in protection (Cherry et al. 1998), and no single measure seemed to assure protection.

Despite an uncertain understanding of the correlates of immunity associated with aP vaccines, several formulations were licensed for use in the US by 1991 (Advisory Committee on Immunization Practices 1997) and contain a range of proteins including FHA, PRN, FIM-2, FIM-3, and inactivated pertussis toxoid. Current US recommendations for children include a 5-dose schedule of DTaP (diphtheria, tetanus, acellular pertussis) through 4–6 years of age, with a Tdap booster (containing reduced content of both the diphtheria and pertussis components) at 11–12 years of age (Faulkner et al. 2015). Initial estimates of vaccine efficacy appeared promising and ranged from 84–89%, and use of the aP vaccine was recommended for all vaccinations by 1997 (Advisory Committee on Immunization Practices 1997), with the wP vaccine phased out soon thereafter. However, in the decades following implementation of the full aP vaccine schedule, an alarming rise in pertussis cases was observed in several geographical regions including North America, Australia and Europe (Plotkin 2014). Based on the close proximity in time between the resurgence of pertussis and the switch to the aP formulation, Australian researchers examined the relative risk for children developing pertussis based on their immunization history with either the wP or aP vaccines (Sheridan et al. 2012). Their study found that children who received a full aP vaccine schedule had a 3.29-fold increase (95% CI 2.44–4.46) in annual reporting rates for pertussis versus their wP-vaccinated counterparts. Furthermore, in mixed vaccination series (i.e., children receiving both wP and aP formulations) they found that the order of the vaccination series had a substantial impact on outcome, with aP primo-vaccinated children still demonstrating deficits in protection even when given the wP vaccine in later booster doses. This study has been supported by evidence from several US cohorts (Liko et al. 2013; Klein et al. 2013). In Oregon, analysis of children immunized during the transition from DTwP to DTaP demonstrated that priming with the acellular vaccine consistently increased the risk of contracting pertussis by ~2-fold across multiple vaccine booster scenarios (Liko et al. 2013). A case-control study performed in California indicated that teenagers who had received four doses of DTaP versus DTwP formulations during their initial vaccination series had a nearly 6-fold increased risk of contracting PCR-positive pertussis (Klein et al. 2013).

While the underlying cause of poor protective efficacy is unclear, waning immunity may play a key role. A large-scale assessment of the 5-dose DTaP schedule used in the US estimated VE as a function of time (Misegades et al. 2012). This study found VE ranging from 92.3–98.1% during the first 3 years following the final booster dose, but this decreased over time to as low as 71.2% at time points >5 years post-vaccination. In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended adding a Tdap booster at 11–12 years of age in an attempt to counteract this waning immunity (Faulkner et al. 2015). However, boosting immunity in adolescents again appears to be limited. In California, researchers estimated VE of only 68.8% (95% CI 59.7 to 75.9) during the first year after Tdap vaccination of adolescents, dropping to as low as 8.9% (95% CI – 30.6 to 36.4) by the fourth year (Klein et al. 2016). Studies in both Wisconsin (Koepke et al. 2014) and Washington (Acosta et al. 2015) substantiate these results, with VE ranging from 73.3%–75% during the first year following vaccination, but rapidly waning to 11.9%–34% within just a few years. The answer to this public health problem is unclear. A range of potential solutions have been proposed and although a return to the old wP vaccine is considered unlikely (Plotkin 2014), new wP vaccines with high efficacy and improved safety profiles

might still be a viable option. Increasing antigen doses may improve immunogenicity since VE differences have been observed between different Tdap manufacturers, with higher antigen doses associated with increased VE (Koepke et al. 2014). However even with increased antigen dose, VE still wanes rapidly, pointing to what may be a fundamental limitation of the current acellular vaccine approach. Until researchers can find an improved approach to elicit durable immunity while retaining an acceptable safety profile, pertussis will represent a continuing problem for the foreseeable future.

5. Partially successful vaccines

In addition to examples of successful vaccines and clear vaccine failures, there are also a large number of partially successful vaccines. We define a vaccine as “partially successful” if it elicits a protective immune response against a particular pathogen with efficacy rates that are near or substantially less than 50%. Challenging pathogens, such as those with multiple serotypes, complex lifecycles, or high antigenic variability are the ones that are most likely to have vaccine counterparts that are either non-existent or only partially successful. Some examples of challenging pathogens with partially successful vaccine candidates include (a) dengue virus (DENV) with its 4 inter-related serotypes, (b) VZV representing a latent herpesvirus that causes chickenpox (primary infection) or shingles (after reactivation/re-exposure), (c) *Plasmodium*, a parasite with a complex multi-stage lifecycle that causes malaria, and (d) human immunodeficiency virus (HIV), a retrovirus with a complex lifecycle as well as high antigenic variability.

5.1 Dengue virus

DENV is a mosquito-borne pathogen that is ubiquitous throughout tropical regions of the world and endemic or epidemic in 154 countries (Furuya-Kanamori et al. 2016). DENV infection may result in a spectrum of disease ranging from acute, debilitating febrile illness (dengue fever, DF) to severe, life-threatening hemorrhagic disease (dengue hemorrhagic fever, DHF; dengue shock syndrome, DSS). Within DENV, there are 4 serotypes (DENV1, DENV2, DENV3, and DENV4), and each has been found to cause human disease and mortality. Current estimates indicate that nearly 4 billion people are at risk (Brady et al. 2012), with disease burden ranging from 58–96 million apparent DENV infections per year (Bhatt et al. 2013; Stanaway et al. 2016), resulting in approximately 500,000 cases of DHF/DSS and greater than 20,000 deaths (Murray et al. 2013). Infection with one DENV serotype is known to provide durable protective immunity against reinfection by that particular serotype (Webster et al. 2009). However, immunity to one DENV serotype may predispose an individual to more severe disease if infected by a second DENV serotype through a process believed to be associated with antibody-dependent enhancement (ADE) of infection of Fc- γ receptor-bearing cells (Guzman et al. 2000; Burke et al. 1988; Vaughn et al. 2000; Guzman et al. 1987; Halstead et al. 1970). Although the role of ADE in DHF/DSS has been questioned in recent years (Webster et al. 2009), this concept nonetheless remains an important consideration in terms of vaccine development. As such, it is widely accepted that an optimal DENV vaccine must provide protection against all 4 serotypes to provide broad antiviral immunity and to prevent the potential complications of ADE.

Dengvaxia® is a live, attenuated tetravalent vaccine that consists of four chimeric yellow fever virus strain 17D (YFV-17D) vectors expressing the DENV envelope and premembrane proteins of each DENV serotype, and has recently become the first licensed DENV vaccine (Sanofi Pasteur 2016). Despite the excitement surrounding this major milestone, concerns have emerged over efficacy and safety (Simmons 2015; Halstead and Russell 2016). An initial Phase IIb trial conducted in Thailand estimated an overall VE of only 30.2% (95% CI - 13.4– 56.6) and the primary estimate of efficacy was not significant (Sabchareon et al. 2012). When segregated by serotype, there was some indication of efficacy for DENV1, DENV3 and DENV4, whereas with DENV2 (which constituted the majority of cases among vaccinated and controls) the vaccine demonstrated no protection. Larger Phase III trials in both Asia (Capeding et al. 2014) and Latin America (Villar et al. 2015) have now demonstrated modest protection against DENV, with VE ranging from 56.5–60.8%. However, as suggested in the Phase IIb trial, both studies demonstrated differences among serotypes, with DENV2 again showing the lowest protective immunity (35.0–42.3% VE). More concerning may be the limited protection observed in younger subjects, and those who were seronegative at the time of vaccination. In the Asian trial, participant age ranged from 2–14 years old, and decreasing efficacy was closely tied to decreasing age, with 2–5 year old children demonstrating only 33.7% VE (95% CI 11.7–50.0) (Capeding et al. 2014). The Latin American trial only recruited children 9–16 years of age, and found similar efficacy across this range (Villar et al. 2015). Across both Phase III trials, while VE in seropositive children ranged from 74.3–83.7%, it was sharply lower among previously seronegative children (VE = 35.5–43.2%) (Capeding et al. 2014; Villar et al. 2015). This suggests the age dependence observed in the Asian trial may be tied to the rates of seropositivity prior to vaccination within age groups (i.e., younger children have a lower likelihood of prior exposure to wild type DENV). Seronegative children demonstrated neutralizing antibody titers that were typically ~10-fold lower than their seropositive counterparts after vaccination (Table S8 in (Villar et al. 2015)), and this limited immune response could play a role in the low observed VE. Unfortunately, this still leaves unexplained why seronegative children were unable to mount a robust immune response even after 3 immunizations spaced every 6 months. These results likely underlie the current recommendation to immunize only children 9 years of age (Sanofi Pasteur 2016). Unfortunately, this leaves a substantial gap in coverage, especially considering that younger children represent a vulnerable population that experience the highest rates of severe complications following DENV exposure (Guzman et al. 2002).

Formal estimates of Dengvaxia VE have been limited to one year following the completion of the vaccination series. Ongoing long-term safety analyses have been described (Hadinegoro et al. 2015) and will monitor hospitalization rates for DENV illness in vaccinees and controls for up to 6 years. Through 3–4 years post-vaccination (depending on the trial), there appears to be a retained benefit for children vaccinated at 9–16 years of age (Hadinegoro et al. 2015). Conversely, there may also be a risk of increased hospitalizations for younger subjects, especially those who were 2–5 years old at the time of vaccination. Whether or not this points to enhanced disease among children with suboptimal immune responses remains uncertain, though it has been noted that the frequency of severe forms of DENV (such as DSS) do not appear to be increased in this age group (Simmons 2015).

Nevertheless, given the relatively modest efficacy of the vaccine and substantial age restrictions, DENV continues to pose a global threat with limited solutions.

5.2 Varicella zoster virus

Following the initial 82–86% success rate of the live attenuated VZV vaccine for prevention of varicella (i.e., chickenpox) in children after a single dose (Izurieta et al. 1997; Vazquez et al. 2001; Lopez et al. 2006), it was assumed that a similar approach would be successful for protection of older individuals (> 60 years of age) against herpes zoster (i.e., shingles). However, in a pivotal randomized double-blinded clinical trial involving 38,546 adults monitored for a median of 3.12 years, the Oka/Merck VZV vaccine provided 51.3% efficacy against clinical diagnosis of herpes zoster (Oxman et al. 2005). Vaccine efficacy was higher among younger subjects (63.9%) but reached only 37.6% efficacy in subjects 70 years of age or older – indicating that the vaccine performed poorly in the aged population at most risk for developing severe herpes zoster and post-herpetic neuralgia. In 2006, the ACIP recommended a single dose of vaccine against herpes zoster (Harpaz et al. 2008) but in 2013, the ACIP declined to recommend the vaccine for younger adults 50–59 years of age due to the limited amount of information regarding the durability of protection after vaccination (Tseng et al. 2016). Indeed, several studies found evidence of rapidly declining protection (Morrison et al. 2015; Schmader et al. 2012; Tseng et al. 2016) with the most compelling evidence presented in a study comparing 176,078 vaccinated subjects to 528,234 unvaccinated subjects who were followed for up to 8 years after vaccination (Tseng et al. 2016). Although vaccine efficacy approached 69% during the first year after vaccination, protective immunity declined rapidly thereafter with just 4% vaccine efficacy by the 8th year after immunization. The decline in protection against disease was similar among vaccine recipients aged 60–69 years and those aged ≥ 70 years, indicating that advanced age itself was not responsible for the decline in protective immunity.

Although no proven correlate of protective immunity exists for herpes zoster, a long-held belief has been that loss of antiviral T cell-mediated immunity is the determining risk factor for disease onset (Kost and Straus 1996; Wilson et al. 1992; Miller 1980). Along these lines, studies demonstrated that VZV vaccination resulted in a substantial increase in T cell-mediated immunity (Oxman 1995; Levin et al. 2003) and the dose of vaccine for prevention of herpes zoster (approximately 14-fold higher than the dose administered during primary vaccination to prevent varicella) was chosen on the basis of its ability to elicit a significant increase in antiviral T cell immunity among older adults (Oxman et al. 2005). Bearing in mind that the first-line approach of using a live attenuated strain of VZV for vaccination would be the most likely candidate for eliciting strong antiviral T cell responses, one would have found little support for the use of a non-replicating subunit vaccine since it would presumably be far less likely to elicit the T cell responses that develop following infection with a live attenuated version of the same virus. Nevertheless, conventional wisdom was displaced by the success of a non-traditional approach to vaccination against herpes zoster with a subunit vaccine consisting of a single viral protein antigen, recombinant VZV glycoprotein E (gE) (Lal et al. 2015). In this study involving 15,411 subjects (7,698 vaccinated and 7,713 placebo controls) who were followed for a mean of 3.2 years, vaccine efficacy was 97.2%. There was also no age-associated reduction in vaccine efficacy among

subjects 70 years of age. This indicated that the immunosenescence and age-associated reduction in vaccine efficacy observed after live VZV vaccination could be overcome with a simple 2-dose regimen of a non-replicating subunit vaccine. Further analysis of the subunit vaccine-induced VZV gE-specific CD4⁺ T cell responses and gE-specific antibody responses indicates that immunity initially declines for the first 1–2 years after vaccination but then reaches a plateau that is maintained for at least 6 years. In these studies, CD4⁺ T cell memory was sustained at nearly 4-fold higher than pre-vaccination levels and antiviral antibody responses remain approximately 7-fold higher than pre-vaccination levels (Chlibek et al. 2016). Together, these results indicate that this simple subunit vaccine has the potential to provide long-lasting immunity against herpes zoster.

5.3 Plasmodium

Plasmodium parasites are the causative agent of malaria and the complex lifecycle of this parasite has been problematic for the development of an effective vaccine. The human host is infected by sporozoites transmitted by infected mosquitos. The sporozoites travel through the bloodstream and infect hepatocytes where they reproduce as merozoites. The merozoites infect and multiply in new red blood cells that lyse to release more merozoites and initiate the next round of infection. Some merozoites develop into the precursors of male and female gametes, which can infect a feeding mosquito and mature, fuse to form fertilized ookinetes, and develop into sporozoites that travel to the salivary glands where they can be transmitted to the next human host during blood feeding. The invading sporozoites that are transmitted by infected mosquitos represent the best vaccine target since blocking infection at the earliest stage of transmission is likely to provide the highest clinical benefit. The most advanced malaria vaccine candidate is RTS,S, a subunit vaccine based on a *Plasmodium* circumsporozoite protein (CSP) that is genetically fused to hepatitis B virus surface antigen. The vaccine has been in development for more than 30 years (Kaslow and Biernaux 2015) and has advanced through Phase III clinical trials. Protection against clinical malaria in children (ages 5–17 months) after 3 doses of vaccine is modest; vaccine efficacy reached 45.1% during the first 0–20 months after vaccination but waned rapidly, with only 16.1% vaccine efficacy observed during months 21–32 in young children. The levels of protection are even lower among infants (ages 6–12 weeks) with only 27.0% protective efficacy at 0–20 months with immunity falling to near negligible levels (7.6%) from 21–32 months after vaccination (RTS-S Clinical Trials Partnership 2015). The partial success among children and the weak protective immunity elicited among infants indicates that this subunit vaccine is unable to reliably protect the most vulnerable populations who are at the highest risk for severe cases of malaria and this is compounded by the lack of durable immunity even after a 3-dose regimen.

An alternative approach to malaria vaccination that has gained recent attention utilizes intact gamma-irradiated sporozoites purified from infected mosquitos (Richie et al. 2015; Hoffman et al. 2015). The main advantage of this approach is that vaccination is performed using the whole organism in which many potentially immunogenic proteins are presented in their native conformation. In a human challenge model of *Plasmodium* infection, the highest administered dose provided 100% protection from parasitemia for 6 immunized subjects (Seder et al. 2013). The main disadvantages to this approach are that direct intravenous

injection of the vaccine is required (early studies involving subcutaneous or intradermal vaccination failed (Epstein et al. 2011)) and there are technical limitations to the production, purification, and long-term stability of sporozoites prepared from *Plasmodium*-infected mosquitos. Another potential concern is that the vaccine may be on the knife's edge in terms of protective efficacy since a 4-dose vaccination schedule elicited promastigote-specific antibodies that were roughly half of that obtained from a 5-dose schedule and similarly, protection from clinical disease declined from 100% (6/6 subjects) to 60% (6/9 subjects). Since many vaccine-mediated immune responses decline by 2- to 10-fold from their peak levels before reaching a plateau stage of more stable long-term maintenance, it is possible that this vaccine approach may lose at least some protective efficacy over a relatively short period of time. Nevertheless, the results of these studies provide a foundation on which future vaccines may be developed that elicit appropriate immune responses that block the earliest stages of *Plasmodium* infection and further studies are currently underway (Hoffman et al. 2015).

5.4 Human immunodeficiency virus

HIV, the causative agent of Acquired Immune Deficiency Syndrome (AIDS), is a notoriously difficult vaccine target and of the 6 field efficacy trials that have been performed to date, all HIV vaccines have failed except one, the RV144 vaccine (Kim et al. 2015). The RV144 trial involved 16,402 subjects and a prime-boost strategy utilizing a recombinant canarypox vector expressing HIV Gag, pro, and envelope administered at 0, 1, 3, and 6 months in addition to alum-adjuvanted monomeric envelope proteins co-administered at the 3 and 6 month time points. Vaccine efficacy reached 60.5% at 1 year after vaccination but declined to 31.2% efficacy at 3.5 years after vaccination (Kim et al. 2015). Despite these suboptimal results, any significant protection against HIV is encouraging and current clinical trials involve redesigned gp120 envelope constructs, comparison of different adjuvants (MF59 and AS01B) and a revised vaccination schedule that includes a booster dose administered at 12 months (Gray et al. 2016). Moreover, development of intact HIV envelope trimers provide a new approach to HIV vaccine development and further studies are planned to test multiple trimers in either simultaneous or sequential combinations in order to optimally induce high titer, broadly neutralizing antibodies (de Taeye et al. 2016). Regardless of the approach that is taken, development of a vaccination strategy that induces long-term immunity above a protective threshold (preferably with broadly neutralizing antibodies (Burton and Mascola 2015)) is a high priority and likely to be key to the success of any future HIV vaccine.

6 Future vaccines for challenging pathogens

Despite the ultimate goal of performing rationale vaccine design in which a deeper understanding of pathogen structure, immunogenicity, and pathogenesis is utilized in the construction of a new vaccine, many of our current successful vaccine strategies have been developed empirically. In some cases such as measles, mumps, and rubella, an attenuated version of the target virus provides safe and effective vaccine-mediated protection. In other cases, successful vaccine development was counterintuitive to the approach that one might have predicted based on the characteristics of the pathogen itself. HPV for example,

represents a mucosal pathogen that evades the immune system in order to sustain a chronic, essentially lifelong infection within its human host. One might have predicted that a mucosal route of vaccination would be preferred, that CD8⁺ T cells would be the most important cell type for protecting against intracellular pathogens, and that antiviral IgA responses might be much more important than IgG responses in terms of protecting mucosal sites from natural infection. In contrast to these a priori expectations, development of non-replicating HPV VLP vaccines that are administered by intramuscular injection induce strong IgG responses and relatively minor IgA or T cell responses but still provide sustained protective immunity against HPV for many years after vaccination. This result would not have been predicted based on conventional wisdom and knowledge of the natural host: pathogen interactions and provides an interesting counterpoint showing that sometimes it is important to take empirical approaches to the development of vaccines to the most complex pathogens.

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Table 1.

Licensed vaccines

Live, attenuated vaccines

Adenovirus, Types 4 and 7

Dengue virus^a

Influenza virus

Measles virus

Mumps virus

*Mycobacterium tuberculosis*Poliovirus^b

Rotavirus

Rubella virus

Salmonella typhi (typhoid fever)

Varicella zoster virus (chickenpox and shingles)

Variola virus (smallpox)

Yellow fever virus

Non-Replicating microbial particle vaccines*Bordetella pertussis*^c (whooping cough)

Hepatitis A virus

Hepatitis B virus

Human papillomavirus

Influenza virus^d

Japanese encephalitis virus

Neisseria meningitidis serogroup B^e (bacterial meningitis)

Poliovirus

Rabies virus

Tick-borne encephalitis virus^f*Yersinia pestis*^g (bubonic plague)**Subunit vaccines***Bacillus anthracis* (anthrax)*Bordetella pertussis* (whooping cough)

Diphtheria toxin

Haemophilus influenzae type b

Influenza virus

Neisseria meningitidis serogroups A, C, Y, W-135 and B^e (bacterial meningitis)*Salmonella typhi* (typhoid fever)*Streptococcus pneumoniae* (pneumococcal disease)

Tetanus toxin

^aAs of April 4, 2016 the Dengvaxia® live attenuated chimeric vaccine was licensed for use in Mexico, El Salvador, the Philippines and Brazil (Sanofi Pasteur 2016).

^b In the US, the oral poliovirus vaccine (OPV) was fully replaced by the inactivated poliovirus vaccine (IPV) by 2000 (Advisory Committee on Immunization Practices 2000).

^c The whole-cell pertussis (wP) vaccine was recommended to be fully replaced by the acellular pertussis (aP) vaccine by 1997 in the US, but continues to be used routinely in other countries (Advisory Committee on Immunization Practices 1997).

^d A whole-virion inactivated H5N1 pandemic influenza vaccine (Vepacel®) is licensed for use in the EU (Plosker 2012).

^e The Bexsero® meningococcal group B vaccine uses a combination of outer membrane vesicle particles as well as individual recombinant proteins (Novartis Vaccines and Diagnostics 2015).

^f A tick-borne encephalitis virus vaccine is not currently licensed for the US, but is used in multiple EU countries (Heinz et al. 2013).

^g Manufacture of the plague vaccine in the US was discontinued in 1999 (Williamson and Oyston 2013).