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Review

Wanted, dead or alive: New viral vaccines

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ABSTRACT

Vaccination is one of the most effective methods used for protecting the public against infectious disease. Vaccines can be segregated into two general categories: replicating vaccines (i.e., live, attenuated vaccines) and non-replicating vaccines (e.g., inactivated or subunit vaccines). It has been assumed that live attenuated vaccines are superior to non-replicating vaccines in terms of the quality of the antiviral immune response, the level of protective immunity, and the duration of protective immunity. Although this a prevalent viewpoint within the field, there are several exceptions to the rule. Here, we will explore the historical literature in which some of these conclusions have been based, including "Experiments of Nature" and describe examples of the efficacy of replicating vaccines compared to their non-replicating counterparts. By building a better understanding of how successful vaccines work, we hope to develop better "next-generation" vaccines as well as new vaccines against HIV—a pathogen of global importance for which no licensed vaccine currently exists.

Contents

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1. Introduction

The remarkable success of vaccination against a wide spectrum of human pathogens represents one of the great achievements in medicine. In this regard, there is no doubt that live vaccines have played a critical role in controlling many human diseases. The world's first vaccine was developed against smallpox by Edward Jenner (Jenner, 1798, 1799, 1800) and this breakthrough eventually led to the eradication of natural smallpox (Fenner et al., 1988). Live vaccines have been important in controlling other pathogens including polio (Sabin vaccine, introduced in 1961) and yellow fever virus (introduced in 1936). However, these important advances have not come without a price; smallpox vaccination of the general public resulted in 1–8 deaths per million vaccinations between the 1940s through the 1980s (Kretzschmar et al., 2006). Routine vaccination of civilians was therefore discontinued worldwide in 1980 when the World Health Organization confirmed the global eradication of smallpox. Likewise, routine vaccination with the live oral polio vaccine (OPV) resulted in an average of 9 cases of vaccine-associated paralytic poliomyelitis (VAPP) each year from 1961 to 1989 in the US (Alexander et al., 2004). More recently, OPV vaccination campaigns in Nigeria have also resulted in at least 69 cases of VAPP (CDC, 2007). With these safety concerns, the US replaced the live polio vaccine entirely with the inactivated polio vaccine (IPV) in 2000 and this has led to the complete elimination of VAPP (Alexander et al., 2004). The current yellow fever vaccines (yellow fever 17D or 17DD strains) result in 1–2 deaths per million doses administered (Kitchener, 2004; Lindsey et al., 2008; Struchiner et al., 2004) including fatalities among young, otherwise healthy adults (Doblas et al., 2006; Gerasimon and Lowry, 2005; Vasconcelos et al., 2001). Although the yellow fever vaccine has been described as one of the safest vaccines ever developed, it has been contraindicated in infants since the 1960s due to high rates of encephalitis (Monath, 2004; Sencer et al., 1966) and viscerotropic disease (with ~50% mortality) occurs in the elderly at an alarming rate of 1 per 50,000 doses (Barrett et al., 2007; CDC, 2005b; Lindsey et al., 2008).

Safety concerns explain why some live attenuated vaccines are eventually replaced by non-replicating or inactivated vaccines (Fig. 1). In general, this represents an evolutionary process; prior to the development of a specific vaccine, people developed immunity by natural infection with wild-type circulating pathogens. In some cases, the infection and disease outcome could be modified by the route of exposure or the age of exposure. Prior to the development of the smallpox vaccine by Edward Jenner, a type of immunization described as "variolation" was practiced. This procedure involved inoculation of a patient's skin with smallpox (variola virus), which resulted in only 0.5–1% mortality in comparison with the natural route of exposure via the respiratory route, which resulted in approximately 30% mortality. Age at the time of infection can play a substantial role in disease outcome. Prior to licensure of the current varicella zoster virus (VZV, i.e., chickenpox) vaccine, it was not uncommon for parents to expose their young children to other VZV-infected children on purpose in order for them to be infected with the virus at a younger age when the disease severity is much less than what is typically observed during primary VZV infection as an older adolescent or as an adult. Induction of immunity through natural infection is often first replaced by vaccine-mediated immunity derived from live, attenuated vaccines. This approach, in turn, may later be replaced by the use of an inactivated or subunit vaccine—especially if there are common (or even rare) severe adverse events (AEs) associated with the original live vaccine. This process may be dictated to a large degree by the spread and severity of the disease itself and the means used to treat it. When smallpox was endemic, the one in a million chance of vaccine-associated death was small compared to the 30% mortality of the disease itself. However, once smallpox was eradicated, the risk:benefit ratio changed sharply. The rare but sometimes severe AEs associated with smallpox vaccination overshadowed its protective use in the absence of an outbreak situation and this resulted in the interest to develop a second generation tissue culture-based vaccine as well as a third-generation non-replicating vaccine based on Modified Vaccinia Ankara (MVA). Likewise, once polio was no longer endemic in the US, the risk of live virus vaccination became higher than the risk of the disease itself—resulting in the shift from using the live attenuated oral Sabin vaccine to the injected Salk vaccine comprised of inactivated virus. The evolution from natural infection to live attenuated vaccines to inactivated vaccines is by no means a universal process. In some cases, such as the Hepatitis B vaccine, the safety and efficacy of the subunit vaccine allowed its routine use without a live attenuated intermediate vaccine being pursued. In contrast, the remarkably high safety profile of the live attenuated measles–mumps–rubella (MMR) vaccine (Amanna and Slifka, 2005) indicates that it is unlikely to be replaced by an inactivated vaccine formulation any time soon.

There remains considerable controversy over the efficacy and use of live vaccines versus inactivated or subunit vaccines. One concern is whether inactivated vaccines can stimulate protective mucosal immunity. A study of 527 infants given the oral polio vaccine (OPV) or IPV followed by OPV demonstrated that partial mucosal immunity was observed after vaccination with IPV (Laassri et al., 2005). Following IPV immunization, there was a 35–56% reduction in the number of infants who shed virus (depending on the serotype) following infection with OPV. Of the IPV-immunized infants who shed virus, the fecal titers were much lower (reduced by 75%). One caveat to this study however, is that two doses of IPV may not have provided the full immunity that is observed after the standard 3-dose schedule. Although IPV may not be as effective as prior OPV immunization in preventing/reducing fecal virus shedding, it is administered by either the intramuscular or

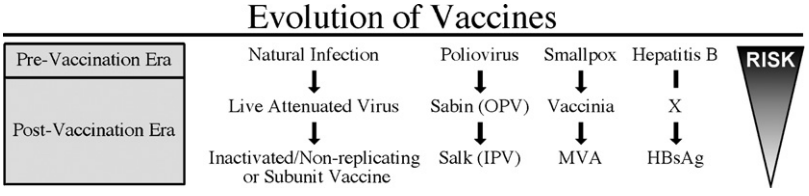

Fig. 1. Evolution of vaccines. Prior to the introduction of vaccines, immunity developed following natural infection with a specific viral pathogen. Live attenuated vaccines often are developed from the wild-type pathogen after selecting for less virulent strains that are able to infect the host and elicit antiviral immunity, but with greatly reduced disease severity. In cases in which live attenuated vaccines have rare but serious adverse events, further refinement of the vaccine is provided by developing an inactivated formulation for immunization. This may consist of a whole virus vaccine that has been inactivated by formaldehyde (e.g., IPV), use of a non-replicating strain of virus (e.g., MVA), or replacement with a subunit vaccine consisting of only one or a few protective antigens (e.g., Hepatitis B surface antigen). The risk of morbidity or mortality is reduced as the immunogenic insult is modified from natural infection to attenuated infection, to immunization with an inactivated or non-replicating antigen. In some cases, such as in the development of the Hepatitis B vaccine, the intermediate step involving the development of an attenuated vaccine may be omitted if a non-replicating vaccine provides effective immunity. Abbreviations: OPV; live oral polio vaccine; IPV; inactivated polio vaccine; MVA; modified vaccinia Ankara.