Vaccine 32 (2014) 2948–2957

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

How advances in immunology provide insight into improving vaccine efficacy

Mark K. Slifka[a,*], Ian Amanna[b]

[a] Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Sciences University, 505 NW 185th Avenue, Beaverton, OR 97006, USA
[b] Najít Technologies, Inc., 505 NW 185th Avenue, Beaverton, OR 97006, USA

ARTICLE INFO

Article history:
Received 31 December 2013
Received in revised form 13 March 2014
Accepted 25 March 2014
Available online 5 April 2014

Keywords:
Vaccination
Immunological memory
Antibody
Protection

ABSTRACT

Vaccines represent one of the most compelling examples of how biomedical research has improved society by saving lives and dramatically reducing the burden of infectious disease. Despite the importance of vaccinology, we are still in the early stages of understanding how the best vaccines work and how we can achieve better protective efficacy through improved vaccine design. Most successful vaccines have been developed empirically, but recent advances in immunology are beginning to shed new light on the mechanisms of vaccine-mediated protection and development of long-term immunity. Although natural infection will often elicit lifelong immunity, almost all current vaccines require booster vaccination in order to achieve durable protective humoral immune responses, regardless of whether the vaccine is based on infection with replicating live-attenuated vaccine strains of the specific pathogen or whether they are derived from immunization with inactivated, non-replicating vaccines or subunit vaccines. The form of the vaccine antigen (e.g., soluble or particulate/aggregate) appears to play an important role in determining immunogenicity and the interactions between dendritic cells, B cells and T cells in the germinal center are likely to dictate the magnitude and duration of protective immunity. By learning how to optimize these interactions, we may be able to elicit more effective and long-lived immunity with fewer vaccinations.

1. Introduction: Success of current vaccines

It is difficult to over-emphasize the role that vaccines have played in public health by controlling infectious disease, improving the quality of life and increasing life expectancy. For example, analysis of the impact of immunization with 7 of the 12 vaccines administered during routine childhood immunization in 2001 revealed that within a single US birth cohort, these vaccines prevent 33,000 deaths and 14 million cases of disease [1]. In addition to reducing morbidity and mortality, this program of routine childhood vaccination is estimated to result in societal cost savings of nearly $33 billion that would otherwise be lost due to hospitalization, disability, and loss of productivity. The 2001 US immunization schedule involved 12 vaccines, including ones against measles, mumps, rubella (collectively known as MMR), tetanus and diphtheria toxoids, acellular pertussis, *Haemophilus influenza* B, polio, hepatitis B virus, a pneumococcal conjugate, influenza, and varicella zoster virus. In addition to these vaccines, the 2013 immunization schedule (http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a2.htm) also includes vaccines against rotavirus, hepatitis A virus, human papilloma virus, and meningococcal disease. The addition of these vaccines will undoubtedly further increase the cost-benefit ratios of routine childhood immunization as well as providing further reductions in disease and mortality.

From a historical perspective, vaccines have dramatically changed the landscape of infectious disease. Polio, measles, and rubella are no longer endemic in the US and smallpox, once arguably the most feared global threat among infectious diseases, is now extinct worldwide. Comparisons between the levels of disease in the pre-vaccine era [2] and the most recent reports on morbidity and mortality for vaccine-preventable diseases [3] show the dramatic influence that routine vaccination can have on human health (Fig. 1). In 2012, there were no reports of polio in the US and cases of measles, mumps, rubella, and *H. influenza* B, have dropped by >99% from the pre-vaccine era. The number of tetanus cases has dropped

Abbreviations: MMR, measles, mumps, rubella; OPV, oral polio vaccine; MVA, modified vaccinia Ankura; VZV, varicella zoster virus; YFV, yellow fever virus.

* Corresponding author. Tel.: +1 503 629 4152; fax: +1 503 629 4153.
E-mail address: slifkam@ohsu.edu (M.K. Slifka).

http://dx.doi.org/10.1016/j.vaccine.2014.03.078
0264-410X/

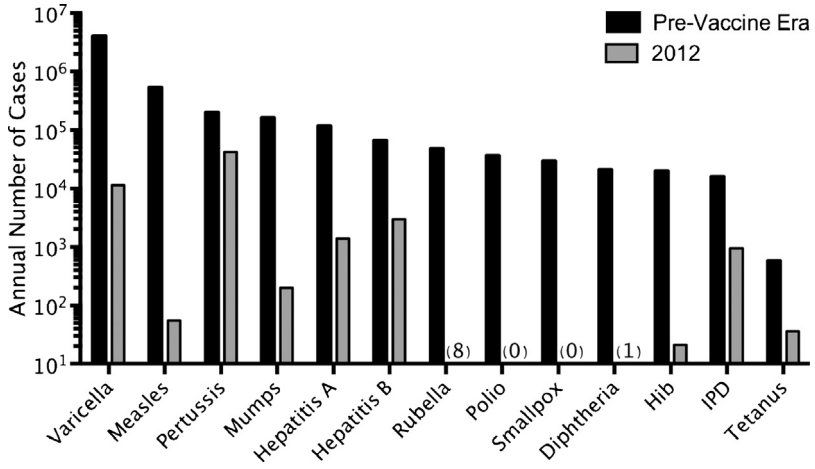

Fig. 1. Vaccination reduces the incidence of infectious disease.
Values represent the number of annual cases of disease that occurred in the United States during the pre-vaccine era (adapted from Ref. [2]) compared to the number of cases for each disease reported to the CDC in 2012 [3]. Invasive pneumococcal disease (IPD, *Streptococcus pneumoniae*) and *Haemophilus influenzae* type b (Hib) case numbers refer to children <5 years of age. Case numbers for polio include both paralytic and non-paralytic forms of the disease. For varicella, the reported incidence in 2012 was 11,477 cases, but this is likely to be underreported due to challenges in clinical diagnosis of milder vaccine-modified cases [92]. For diseases with an incidence of ≤10 cases in 2012, the number of total cases is indicated in parentheses.

by 94% and there have been only two cases of diphtheria reported in the US in the last 10 years. Cases of hepatitis A and hepatitis B have declined by 99% and 96%, respectively. Pneumococcal disease has been reduced by 94% and the incidence of varicella (i.e., chickenpox) has been reduced by >90%. In contrast, *Bordetella pertussis*, the causative agent of whooping cough, represents a continuing and potentially growing concern. While vaccination has reduced the incidence of whooping cough by approximately 79% between the pre-vaccine era and 2012, outbreaks have become progressively larger since the whole-cell pertussis vaccine was replaced by acellular pertussis vaccines consisting of only 2–4 bacterial antigens [4,5]. Although neither natural infection nor vaccination elicit lifelong immunity, the resurgence of this vaccine-preventable disease may be linked to rapidly waning immunity against pertussis despite a 5-dose vaccination regimen [6–8]. The whole-cell pertussis vaccine was self-adjuvanted (i.e., containing bacterial LPS) and induced long-term protection and antibody responses to a broad range of bacterial proteins. However, it was eventually determined to be too reactogenic for routine use and was replaced by acellular pertussis vaccines that are safer, but have recently been found to induce shorter-lived immunity. An interesting study in Australia shows a clear difference in the duration of protective immunity when comparing the whole-cell vaccine to the acellular pertussis vaccine [7]. Moreover, they found that in cases of mixed vaccination regimens, children who first received the whole-cell vaccine had long-lived immunity regardless of whether booster vaccination was performed with whole-cell or the acellular pertussis vaccine. In contrast, if the acellular vaccine was administered first, then booster vaccination with the whole-cell vaccine was much less efficient at eliciting long-term protection, suggesting that initial priming to only a few bacterial antigens may suppress immune responses to a broader array of bacterial antigens upon subsequent exposure [9]. Together, these results show that our overall current vaccine program is effective (Fig. 1), but development of new and improved vaccines that induce durable protective immunity will be essential to the continued success of these vaccination efforts.

2. Duration of immunity depends on the characteristics of the vaccine or infection

Studies describing the duration of immunological memory following acute viral infection date back to the time of Panum, who in 1847, reported that the maintenance of long-term immunity against measles could be sustained for up to 65 years in the absence of re-exposure to the pathogen [10]. Studies by our group [11] previously showed that infection with measles virus results in stable serum antibody responses that are largely maintained above a protective threshold for life (95% confidence interval of antibody half-life; 104 years–infinity). This does not mean that all antibody responses are equally long-lived; indeed, antibody responses to tetanus and diphtheria toxoids showed an 11-year and 19-year half-life, respectively, which is much shorter than that observed for viral infections [11]. An 11-year half-life of tetanus-specific antibodies was also identified by an independent group studying humoral immunity among HIV+ patients [12]. This group not only examined antibody responses to tetanus, but they also performed longitudinal analysis of serum antibody responses to HIV gp120, gp41, and p55 Gag for 7 years after HIV suppression following the initiation of antiretroviral therapy. Interestingly, the antibody responses to HIV envelope antigens, gp120 and gp41, declined rapidly during this course of time (half-life of 81 weeks and 31 weeks, respectively), whereas antibody responses to HIV p55 Gag were more stable, with an approximate half-life of 12.5 years [12]. The shorter antibody half-life to HIV envelope antigens may be linked to their immunosuppressive characteristics [13]. On the other hand, unlike gp120 and gp41 monomers, p55 Gag forms multivalent particulates containing 1500–1800 p55 Gag molecules [14] and these types of complex structures may be involved with the induction of more long-lived humoral immune responses (discussed further in Section 7). Chronic antigenic stimulation may also result in more short-lived plasma cells and fewer long-lived plasma cells [15,16], but this alone would not explain the differential long-lived response to HIV p55 Gag in comparison with HIV gp120 and gp41. Instead, this work indicates that the duration of serum antibody responses may not only differ between pathogens (e.g., HIV vs. measles) or between specific vaccine antigens (e.g., tetanus vs. diphtheria toxoid), but may also differ between individual antigens within a single pathogen (e.g., HIV gp120 vs. HIV p55 Gag). This suggests that there are antigen-specific characteristics that influence the magnitude and durability of the antibody response to each particular antigen. Further studies are needed and analysis of antibody responses to other chronic infections such as hepatitis C virus after successful antiviral therapy would be particularly interesting to compare to the results observed after HIV infection/antiretroviral