Published in final edited form as:
N Engl J Med. 2013 February 7; 368(6): 551–560. doi:10.1056/NEJMra1204186.

Designing Tomorrow's Vaccines

Gary J. Nabel, M.D., Ph.D.
Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

Vaccines are among the most effective interventions in modern medicine. Ever since Edward Jenner's first use of a vaccine against smallpox in 1796 (see text box), the use of vaccines has become indispensable to the eradication of disease. In the 20th century alone, smallpox claimed an estimated 375 million lives, but since 1978, after the completion of a successful eradication campaign, not a single person has died from smallpox. Today, more than 70 vaccines have been licensed for use against approximately 30 microbes, sparing countless lives (Fig. 1A and 1B).[1,2] Diseases including poliomyelitis, measles, mumps, rubella, and others caused an estimated 39 million infections in the 20th century in the United States, but vaccines have since rendered them uncommon (Table 1).[3,4] The success of this public health intervention emanates not only from the identification of effective vaccines but also from a robust infrastructure for vaccine manufacturing, regulatory and safety oversight, and organized approaches to delivery. Vaccines represent the least expensive and most facile way to protect against devastating epidemics. Society derives economic benefits by preventing hospitalization, avoiding long-term disability, and reducing absence from work. In brief, vaccines provide the most cost-effective means to save lives, preserve good health, and maintain a high quality of life.

Despite this legacy, infectious diseases still extract an extraordinary toll on humans. Vaccines have yet to realize their full potential for several reasons. First, effective vaccines are often not available in developing countries. The Global Alliance for Vaccines and Immunization (GAVI) estimates that every year more than 1.5 million children (3 per minute) die from vaccine-preventable diseases. Second, effective vaccines have not yet been developed for diseases such as human immunodeficiency virus (HIV) infection, tuberculosis, and malaria, which claim the lives of more than 4 million people worldwide each year.[5–7] For nearly all successful licensed vaccines, natural immunity to infection has been shown, and the vaccine mimics the protective immune response. In contrast, for HIV infection, tuberculosis, and malaria, it has been difficult to show preventive immunity. Protection against these pathogens requires a distinct approach to vaccine design, based on an understanding of immunopathogenesis and reliance on animal models. In these cases, the challenge is greater, the development path longer, and the outcome less certain.

> "I have received a copy of the evidence at large respecting the discovery of the vaccine inoculation which you have been pleased to send me, and for which I return you my thanks …. I avail myself of this occasion of rendering you a portion of the tribute of gratitude due to you from the whole human family. Medicine has never before produced any single improvement of such utility. Harvey's discovery of the circulation of the blood was a beautiful addition to our knowledge of the

Address reprint requests to: Dr. Nabel at Sanofi, 640 Memorial Dr., Cambridge, MA 02139, or at gary.nabel@sanofi.com.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org. Since this article was accepted for publication, the author has moved from the National Institutes of Health to Sanofi

> animal economy, but on a review of the practice of medicine before and since that epoch, I do not see any great amelioration which has been derived from that discovery. You have erased from the calendar of human afflictions one of its greatest. Yours is the comfortable reflection that mankind can never forget that you have lived. Future nations will know by history only that the loathsome small-pox has existed and by you has been extirpated."
>
> Letter to Dr. Edward Jenner from Thomas Jefferson, Monticello (May 14, 1805)

Finally, many vaccine technologies are old and ill-suited for a rapid response to emerging outbreaks. For example, influenza vaccines rely largely on 50-year-old technology. Current seasonal influenza vaccines are not always well matched and effective against circulating viral strains.[8] Furthermore, when new strains emerged unexpectedly from an animal reservoir in the 2009 influenza A (H1N1) pandemic, vaccine developers were unprepared for rapid deployment of a new vaccine strain. Thus, although the triumphs of yesterday's vaccines have been heartening, a variety of challenges remain for the vaccines of tomorrow. Yet there are reasons to be optimistic that these challenges can be addressed.

Scientific Discovery in the Current Vaccine Era

Structural Biology and Pathogen Entry

Progress in virology, genetics, synthetic biology, and biotechnology has provided a new set of tools to approach current-day vaccinology. Among currently licensed vaccines, the most consistent biomarker for vaccine efficacy has been the presence of antibodies that neutralize the pathogen. These antibodies are often elicited by natural infection or immunization. Our understanding of the molecular structure of viruses has led to a sophisticated understanding of viral glycoproteins and the specific interactions of antibodies that can inactivate them. The field of structural biology has provided new insights into how such antibodies protect against infection by poliomyelitis, measles, and influenza viruses, as well as human papillomavirus (HPV), among others. This detailed knowledge of the mechanism by which viral glycoproteins mediate entry into host cells can now be applied to pathogens that have not been susceptible to this therapeutic approach (Fig. 2).[9–11] Thus, an understanding of the steps related to entry and survival of pathogens that cause illnesses such as HIV type 1 (HIV-1) infection, tuberculosis, and malaria offers molecular targets that serve both to understand natural infection and to identify highly conserved and invariant structures as targets for broadly neutralizing antibodies.

Rational Vaccine Design

The definition of conserved sites of vulnerability on pathogens provides the basis for structure-based vaccine design. Broadly neutralizing antibodies often recognize highly conserved sites that are susceptible to antibody inactivation. Two pathogens, HIV-1 and influenza virus, have proved to be particularly informative in this regard. For example, analysis of the HIV-1 envelope has revealed at least four discrete sites that represent potential targets for the designs of immunogens (i.e., agents capable of inducing an immune response). These include the CD4-binding site, a glycosylated site in variable regions 1 and 2 (V1V2), glycans on the outer domain, and the membrane proximal external region.

Progress in HIV-vaccine research has been advanced recently by the identification of exceptionally broad and potent neutralizing antibodies to each of these sites. Some monoclonal antibodies neutralize more than 90% of circulating viral strains,[12–17] creating new opportunities for HIV-vaccine development. Similar progress has been made in the identification of broadly neutralizing antibodies directed against diverse influenza viruses. At least two independent sites of vulnerability have been identified, one in the stem region

of the viral spike that helps to stabilize the trimer, the three identical viral hemagglutinin glycoproteins that form this structure, and the other in the receptor-binding region that recognizes sialic acid.[18] The existence of such antibodies provides conceptual support and tools that facilitate the development of universal influenza vaccines intended to protect against a wide array of viruses, not only the circulating seasonal strain.

Knowledge of atomic structure also defines viral proteins to elicit these broadly neutralizing antibodies. For HIV infection, alternative forms of envelope glycoproteins include trimers, monomers, subdomains, and specific peptide loops transplanted onto scaffolds.[19] These candidate vaccines are further modified with the use of protein-design algorithms that are based on bioinformatics[10] in efforts to stabilize the immunogen, better expose the conserved sites, and mask or remove undesired epitopes. Similar strategies are under development for influenza viruses, respiratory syncytial virus, and group B meningococcal strains.[9,11,18,20,21]

Although structure-based rational design offers a promising tool for developing vaccines against recalcitrant pathogens, substantial challenges remain. The proper antigenic structure will not necessarily provide all the information needed to produce a potent immunogen that will elicit an antibody response. Furthermore, many broadly neutralizing antibodies are atypical, with an unusually high degree of somatic mutation or long CDRH3 (third complementarity determining regions of heavy-chain variable) regions; such antibodies may not be readily elicited. Finally, a successful vaccine candidate must be designed to bind the germline antibody precursor, select for the appropriate primary recombinational events, and direct its somatic mutations toward the appropriate mature form.[19]

Interactions between Host and Pathogen

Progress in the field of therapeutic monoclonal antibodies has facilitated the identification of effective targets and led to strategies for their successful use in humans.[22] Dozens of new antibodies directed against HIV-1,[18,19] influenza virus,[21] respiratory syncytial virus,[20] hepatitis C virus,[18] and other microbes have identified critical viral structures and enabled structure-based vaccine design. Moreover, deep sequencing, the ability to generate millions of independent sequences of a gene product (e.g., immunoglobulin), has identified intermediates that are critical for the evolution of broadly neutralizing antibodies and has guided vaccine development.[23] Millions of gene sequences encoding heavy and light chains (the polypeptide subunits of an antibody) within a single individual can be analyzed with the use of bioinformatics to trace a potential critical path for vaccine design (Fig. 3).[23] The overarching goal is to use knowledge of structural biology and antibody evolution to design vaccines that will elicit antibodies of known specificity.[24]

Genomewide sequencing of microbes has also allowed for the rational selection of targets for vaccine development. This approach has identified specific gene products of pathogens as vaccine targets. The expression and evaluation of these immunogens have led to the development of a successful vaccine for group B meningococcal strains through a process known as reverse vaccinology.[25]

Immune Biomarkers of Protection

The human immune response has been analyzed with sensitive high-throughput technologies that allow for systems biologic analysis of gene-expression patterns in lymphocytes and in microbes. Such information not only identifies susceptible microbial targets but also has the potential to define new biomarkers of protective immune responses, termed systems vaccinology.[26] Mechanisms of protection and correlates of immunity can be rigorously explored in relevant animal models, but these properties can be definitively established in humans only through clinical trials and postlicensure surveillance. Such information enables

precise immune activation, minimizes unintended side effects, and maximizes clinical efficacy. Successful protection may require neutralizing antibodies,[18] effective T-cell responses,[27] or possibly a combination of the two.

Dendritic Cells and Adjuvants

Critical to the modulation of the immune response is the presentation of specific antigens to the immune system. Dendritic cells play a central role in this process. Three subgroups of such cells, including two forms of myeloid dendritic cells and one plasmacytoid dendritic cell, each with distinct sets of toll receptors, modulate the response to specific antigens and adjuvants. Traditional vaccines have relied on live-attenuated or inactivated organisms, attenuated bacteria or capsules, or inactivated toxins.[28,29] Progress has been made recently in enhancing immunity through a mechanistic understanding of the biology of dendritic cells and their response to adjuvants.[30] Alternative delivery, including viruslike particles or structured arrays with the use of phage or nanoparticles, also stimulate effective immunity and provide powerful tools to confer protection for a specific pathogen (Fig. 4).

Modes and Sites of Vaccine Delivery

An increasing number of vaccine vectors have become available to induce potent humoral or cellular immunity. Gene-based delivery of vaccine antigens effectively elicits immune responses by synthesizing proteins within antigen-presenting cells for endogenous presentation on major histocompatibility complex class I and II molecules. DNA-expression vectors, replication-defective viruses, or prime-boost combinations of the two[31–35] have proved to be effective in eliciting broadly neutralizing antibodies, especially for influenza viruses.[36,37]

Prime-boost vaccine regimens that use DNA and viral vectors[33] have increased both humoral immunity and memory CD8 T-cell responses.[38] For example, a study of a vaccine regimen consisting of a poxvirus vector prime and protein boost (known as the RV144 trial) provided evidence that the vaccine prevented HIV-1 infection among persons in Thailand.[39] Eliciting immune responses at portals of infection (e.g., in the respiratory and intestinal epithelial surfaces for pathogens such as influenza virus and rotavirus, respectively) may generate more efficient mucosal immunity. Similarly, waning vaccine responses require periodic boosting at defined times, requiring more integrated management of vaccines at all ages. Immunization in the elderly is of substantial concern because immune senescence can lead to a decrease in the responsiveness to vaccination.[40]

Clinical Translation and Implementation

Correlates of Protection and Innovative Clinical Trial Design

The effectiveness of vaccines can be tested only in clinical efficacy trials. In the past, advanced clinical development has been undertaken largely by pharmaceutical companies in an effort to obtain licensure. This process is long, costly, and risky with respect to the likelihood of successful protection. For diseases with a major impact on human health but a limited commercial market, there has been little incentive for drug companies to advance these vaccines. For this reason, government involvement can facilitate success. Funding from the Australian government, for example, catalyzed major advances for cholera and HPV vaccines, along with investments from the U.S. National Institutes of Health. Vaccine trials for HIV infection, tuberculosis, and malaria have been facilitated by clinical and translational infrastructure from the National Institute of Allergy and Infectious Diseases, from the European Union, and by nonprofit organizations including the Bill and Melinda Gates Foundation and the Wellcome Trust. Similarly, the Food and Drug Administration (FDA), the European Medicines Agency, the World Health Organization, and the Centers

for Disease Control and Prevention (CDC) provide regulatory, safety, and efficacy oversight. The infrastructure for clinical trials is costly but can be applied to studies of multiple infectious agents and can reduce impediments to vaccine development by facilitating logistically challenging trials in the developing world and supporting the collection of serum samples and lymphocytes for further scientific analysis.

New strategies are sometimes needed to facilitate licensure. For infections that are sporadic or intermittent, such as West Nile, Ebola, and Chikungunya viruses, it is often not possible to perform field trials to demonstrate clinical efficacy. To address this problem, the FDA has proposed the animal rule,[41] according to which efficacy can be shown in relevant animal species, and immune correlates of protection can be defined. Separate phase 2 studies are then performed in humans with the aim of achieving the same level of immunity, and the bridged immune correlate is used as a criterion for licensure. Although uncertainty would remain about vaccine efficacy in a field setting, this approach allows for the development of vaccines that show a high likelihood of protection but that otherwise would not be developed.

Another impediment has been the inability to identify promising vaccine candidates early in development. Definitive efficacy trials take years to perform, and the ability to advance efficacious vaccines represents a key to success for diverse vaccines, a problem evident in the development of vaccines for HIV infection, tuberculosis, and malaria. A potential solution is to use innovative testing, such as adaptive clinical trial designs.[42–44] This approach allows for the evaluation of multiple vaccine candidates in parallel, looking in real time for early efficacy signals to select candidates for more complete and definitive evaluation.[45] Innovations in clinical trial design may therefore accelerate early decision making and increase the likelihood of identifying successful vaccines.

The RV144 trial of a candidate HIV vaccine in Thailand showed the value of efficacy testing for identifying efficacy signals and correlates of immunity in humans. Despite the modest vaccine efficacy of 31%,[39] investigators found that antibodies to the V1V2 regions of envelope glycoproteins correlated inversely with the risk of infection,[46] an unexpected biomarker that may guide product development. Thus, one way to facilitate implementation of successful efficacy trials is to identify promising candidates in phase 1 trials after defining relevant biomarkers through efficacy trials and from relevant vaccine studies in animals, at the same time maintaining stable support and infrastructure for further testing.

From Licensure to Effective Distribution

Many vaccines are intended for use in the developing world, and the development of clinical infrastructure facilitates the distribution of vaccines in resource-poor settings. Governmental and international vaccination organizations such as GAVI and the United Nations Children's Fund (UNICEF) help provide commercial vaccines in these settings. Another impediment is vaccine acceptance by the public. For example, resistance to vaccination has been encountered during poliomyelitis eradication campaigns in Nigeria, and unfounded concern related to autism has proved to be counterproductive for vaccine utilization and in protecting public health in the United States. Increased vigilance and a constructive response to these concerns are needed to support public confidence in vaccines and optimize their implementation.[47,48] Public–private partnerships can also help to address unmet needs, as exemplified in the development of a meningococcal A vaccine in Africa. Modern vaccine development therefore faces challenges beyond biology, and gaps in implementation must be overcome to realize their full potential.

A Look to the Future

Advances in immunology and microbiology have opened new avenues to improve vaccine efficacy. New technologies offer alternative products. For example, innovation in manufacturing has allowed a shift from egg-based methods to cell-based or recombinant methods, including production from insect or plant cells. The following examples illustrate other promising developments.

Beyond Immunologic Mimicry

Jenner created the successful smallpox vaccine by building on an observation in nature: milkmaids who were exposed to cowpox were resistant to smallpox. Most licensed vaccines similarly use live-attenuated or inactivated natural pathogens (e.g., influenza, measles, mumps, poliomyelitis, or rubella viruses) to elicit protective immune responses. Yet increasingly, microbes that cause diseases such as HIV infection, tuberculosis, and malaria evade human immunity. To counter immune evasion, subdominant immune responses can be generated to highly conserved invariant regions that are vulnerable to the immune system (Fig. 1). Vaccines of the future will go beyond mimicking natural immune responses and must generate unnatural immunity.[9] This goal may be achieved by identifying such targets, validating their susceptibility, and using an expanded arsenal of vaccines to target and expand the otherwise subdominant responses to the core vulnerability of these microbes.

Life-Cycle Management of Vaccines

Whereas vaccines are approved for clinical use in the United States by the FDA, standard practices regarding their efficacy, clinical utility, and public health benefit are made by the Advisory Committee on Immunization Practices (ACIP), through the CDC. The ACIP provides advice intended to reduce the incidence of vaccine-preventable diseases and to increase the safety of vaccines, largely in pediatric populations. Yet there are unmet vaccine needs for persons of varying ages, such as the HPV vaccine recommended for adolescents or the shingles vaccine for the elderly. Immune responses also decline with age and vary according to previous pathogen exposure, suggesting that a systematic view of vaccines be adopted for different stages of life,[40] a life-cycle management concept for vaccines that can maximize protection at all ages.

Next-Generation Vaccines

While vaccines are under development, the ability of selected antibodies to show protection in humans would validate the antibody target as a protective antigen and provide valuable information about serum levels required for protection. Because techniques with respect to monoclonal antibodies have improved production and bioavailability, such antibodies can be used more broadly for passive prevention. Pilot studies have recently been considered for persons at high risk for HIV infection. If these studies show that such therapy is effective, sustained delivery mechanisms could potentially be achieved with gene-based antibody delivery. Adeno-associated viral vectors have shown efficacy in protecting rodents, nonhuman primates, and humanized mice from lentiviral infection.[49,50] However, widespread implementation of this approach is not without its challenges. Notable among them is the need to regulate or extinguish antibody gene expression in the event of unanticipated adverse events, but should this approach succeed with the incorporation of such safeguards, it could fundamentally change strategies of immune protection and speed the delivery and expand the promise of vaccines.

Conclusions

Traditional vaccines have shown unprecedented success in preventing human infectious diseases and preserving public health by alleviating death and suffering from numerous microbial threats. The success of such therapies has heralded the arrival of a new era for vaccines. Increased understanding of human immunity and microbes has catalyzed unprecedented advances that can be adopted to improve public health. Despite continuing challenges, the collective effort of governments and nonprofit organizations to expand the utilization of effective vaccines throughout the world has grown. Scientific, medical, and biotechnologic advances promise to improve the utilization of existing vaccines and expand the horizons for tomorrow's vaccines.

Acknowledgments

I thank Drs. Anthony S. Fauci, Harvey Fineberg, Peter Kwong, John Mascola, and Stanley Plotkin for helpful comments and discussions; Dr. Jeffrey Boyington for structural modeling of influenza hemagglutinin; Greg Folkers for advice regarding the composition of the original figures; Ati Tislerics and Mythreyi Shastri for assistance in the preparation of the manuscript; and Brenda Hartman and Jonathan Stuckey for assistance with molecular graphics.

References

1. Landry S, Heilman C. Future directions in vaccines: the payoffs of basic research. Health Aff (Millwood). 2005; 24:758–69. [PubMed: 15886171]
2. Berkley, S. Getting the miracle of vaccines to those who most need them. Presented at the John Ring LaMontagne Memorial Lecture; May 22, 2012; Bethesda, MD: National Institutes of Health; (http://videocast.nih.gov/summary.asp?live=11173)
3. Impact of vaccines universally recommended for children — United States, 1900–1998. MMWR Morb Mortal Wkly Rep. 1999; 48:243–8. [PubMed: 10220251]
4. Roush SW, Murphy TV. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA. 2007; 298:2155–63. [PubMed: 18000199]
5. World malaria report 2011: fact sheet. Geneva: World Health Organization; (http://www.who.int/malaria/world_malaria_report_2011/WMR2011_factsheet.pdf)
6. 2011/2012 Tuberculosis global facts. Geneva: World Health Organization; (http://www.who.int/tb/publications/2011/factsheet_tb_2011.pdf)
7. Joint United Nations Programme on HIV/AIDS. World AIDS Day report. 2012. (http://www.slideshare.net/UNAIDS/unaids-world-aids-day-report-2011-core-slides-10250153)
8. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012; 12:36–44. [Erratum, Lancet Infect Dis 2012;12:655.]. [PubMed: 22032844]
9. Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine. Nat Med. 2010; 16:1389–91. [PubMed: 21135852]
10. Nabel GJ, Kwong PD, Mascola JR. Progress in the rational design of an AIDS vaccine. Philos Trans R Soc Lond B Biol Sci. 2011; 366:2759–65. [PubMed: 21893538]
11. Scarselli M, Arico B, Brunelli B, et al. Rational design of a meningococcal antigen inducing broad protective immunity. Sci Transl Med. 2011; 3:91ra62.
12. Walker LM, Phogat SK, Chan-Hui PY, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science. 2009; 326:285–9. [PubMed: 19729618]
13. Wu X, Yang ZY, Li Y, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science. 2010; 329:856–61. [PubMed: 20616233]
14. Zhou T, Georgiev I, Wu X, et al. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. Science. 2010; 329:811–7. [PubMed: 20616231]
15. Pejchal R, Doores KJ, Walker LM, et al. A potent and broad neutralizing antibody recognizes and penetrates the HIV glycan shield. Science. 2011; 334:1097–103. [PubMed: 21998254]

16. Scheid JF, Mouquet H, Ueberheide B, et al. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. Science. 2011; 333:1633–7. [PubMed: 21764753]
17. Walker LM, Huber M, Doores KJ, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. Nature. 2011; 477:466–70. [PubMed: 21849977]
18. Burton DR, Poignard P, Stanfield RL, Wilson IA. Broadly neutralizing antibodies present new prospects to counter highly antigenically diverse viruses. Science. 2012; 337:183–6. [PubMed: 22798606]
19. Kwong PD, Mascola JR, Nabel GJ. Rational design of vaccines to elicit broadly neutralizing antibodies to HIV-1. Cold Spring Harb Perspect Med. 2011; 1(1):a007278. [PubMed: 22229123]
20. McLellan JS, Yang Y, Graham BS, Kwong PD. Structure of respiratory syncytial virus fusion glycoprotein in the post-fusion conformation reveals preservation of neutralizing epitopes. J Virol. 2011; 85:7788–96. [PubMed: 21613394]
21. Ekiert DC, Wilson IA. Broadly neutralizing antibodies against influenza virus and prospects for universal therapies. Curr Opin Virol. 2012; 2:134–41. [PubMed: 22482710]
22. Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. Nat Rev Drug Discov. 2010; 9:767–74. [PubMed: 20811384]
23. Wu X, Zhou T, Zhu J, et al. Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. Science. 2011; 333:1593–602. [PubMed: 21835983]
24. Burton DR, Desrosiers RC, Doms RW, et al. HIV vaccine design and the neutralizing antibody problem. Nat Immunol. 2004; 5:233–6. [PubMed: 14985706]
25. Kelly DF, Rappuoli R. Reverse vaccinology and vaccines for serogroup B Neisseria meningitidis. Adv Exp Med Biol. 2005; 568:217–23. [PubMed: 16107075]
26. Rappuoli R, Aderem A. A 2020 vision for vaccines against HIV, tuberculosis and malaria. Nature. 2011; 473:463–9. [PubMed: 21614073]
27. Sullivan NJ, Hensley L, Asiedu C, et al. CD8+ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates. Nat Med. 2011; 17:1128–31. [PubMed: 21857654]
28. Lauring AS, Jones JO, Andino R. Rationalizing the development of live attenuated virus vaccines. Nat Biotechnol. 2010; 28:573–9. [PubMed: 20531338]
29. Delrue I, Verzele D, Madder A, Nauwynck HJ. Inactivated virus vaccines from chemistry to prophylaxis: merits, risks and challenges. Expert Rev Vaccines. 2012; 11:695–719. [PubMed: 22873127]
30. Levitz SM, Golenbock DT. Beyond empiricism: informing vaccine development through innate immunity research. Cell. 2012; 148:1284–92. [PubMed: 22424235]
31. Benmira S, Bhattacharya V, Schmid ML. An effective HIV vaccine: a combination of humoral and cellular immunity? Curr HIV Res. 2010; 8:441–9. [PubMed: 20636279]
32. Hu SL, Abrams K, Barber GN, et al. Protection of macaques against SIV infection by subunit vaccines of SIV envelope glycoprotein gp160. Science. 1992; 255:456–9. [PubMed: 1531159]
33. Mascola JR, Sambor A, Beaudry K, et al. Neutralizing antibodies elicited by immunization of monkeys with DNA plasmids and recombinant adenoviral vectors expressing human immunodeficiency virus type 1 proteins. J Virol. 2005; 79:771–9. [PubMed: 15613305]
34. Wang S, Kennedy JS, West K, et al. Cross-subtype antibody and cellular immune responses induced by a polyvalent DNA prime-protein boost HIV-1 vaccine in healthy human volunteers. Vaccine. 2008; 26:3947–57. [PubMed: 18724414]
35. Tomaras GD, Haynes BF. Strategies for eliciting HIV-1 inhibitory antibodies. Curr Opin HIV AIDS. 2010; 5:421–7. [PubMed: 20978384]
36. Wei CJ, Boyington JC, McTamney PM, et al. Induction of broadly neutralizing H1N1 influenza antibodies by vaccination. Science. 2010; 329:1060–4. [PubMed: 20647428]
37. Ledgerwood JE, Wei CJ, Hu Z, et al. DNA priming and influenza vaccine immunogenicity: two phase 1 open label randomised clinical trials. Lancet Infect Dis. 2011; 11:916–24. [PubMed: 21975270]
38. Butler NS, Nolz JC, Harty JT. Immunologic considerations for generating memory CD8 T cells through vaccination. Cell Microbiol. 2011; 13:925–33. [PubMed: 21501363]

39. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009; 361:2209–20. [PubMed: 19843557]
40. Rappuoli R, Mandl CW, Black S, De Gregorio E. Vaccines for the twenty-first century society. Nat Rev Immunol. 2011; 11:865–72. [Erratum, Nat Rev Immunol 2012;12:225.]. [PubMed: 22051890]
41. Burns DL. Licensure of vaccines using the Animal Rule. Curr Opin Virol. 2012; 2:353–6. [PubMed: 22709520]
42. Emerson SS. Issues in the use of adaptive clinical trial designs. Stat Med. 2006; 25:3270–96. [PubMed: 16906553]
43. Chow, S-C.; Chang, M. Adaptive design methods in clinical trials. Boca Raton, FL: Chapman and Hall/CRC; 2007.
44. Coffey CS, Kairalla JA. Adaptive clinical trials: progress and challenges. Drugs R D. 2008; 9:229–42. [PubMed: 18588354]
45. Corey L, Nabel GJ, Dieffenbach C, et al. HIV-1 vaccines and adaptive trial designs. Sci Transl Med. 2011; 3(79):79ps13.
46. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med. 2012; 366:1275–86. [PubMed: 22475592]
47. Black S, Rappuoli R. A crisis of public confidence in vaccines. Sci Transl Med. 2010; 2(61): 61mr1.
48. Larson HJ, Cooper LZ, Eskola J, Katz SL, Ratzan S. Addressing the vaccine confidence gap. Lancet. 2011; 378:526–35. [PubMed: 21664679]
49. Johnson PR, Schnepp BC, Zhang J, et al. Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys. Nat Med. 2009; 15:901–6. [PubMed: 19448633]
50. Balazs AB, Chen J, Hong CM, Rao DS, Yang L, Baltimore D. Antibody-based protection against HIV infection by vectored immunoprophylaxis. Nature. 2012; 481:81–4. [PubMed: 22139420]

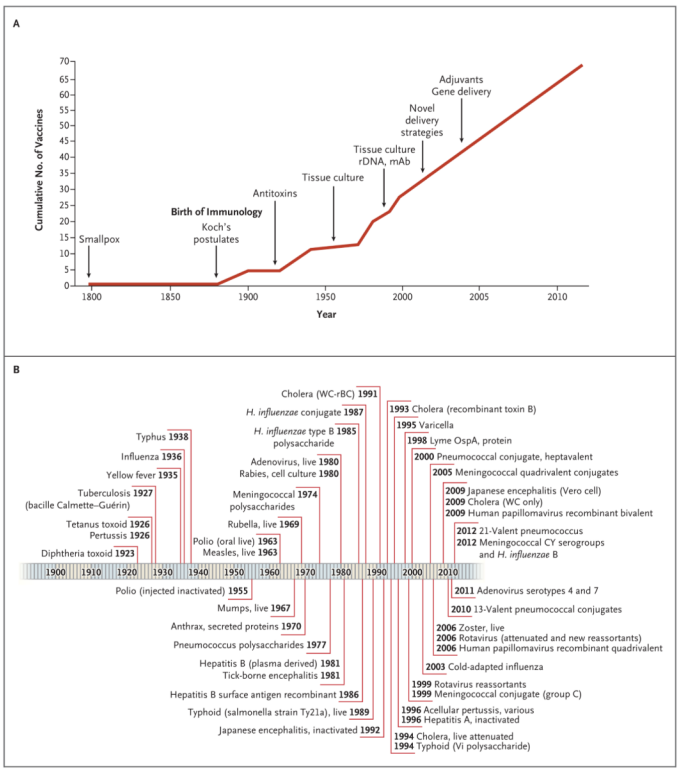

Figure 1. Timelines for Vaccine Development and Licensure of Commercial Vaccines

Panel A shows major milestones and advances in vaccine development and the cumulative number of licensed vaccines since the time of Edward Jenner's first use of a vaccination against smallpox in 1796.[1] Panel B shows the timeline for licensure of commercial vaccines against the indicated pathogens.[2] The abbreviation mAb denotes monoclonal antibody, OspA outer surface protein A, rBS recombinant B subunit of cholera toxin, rDNA recombinant DNA, and WC whole-cell *Vibrio cholerae* O1.

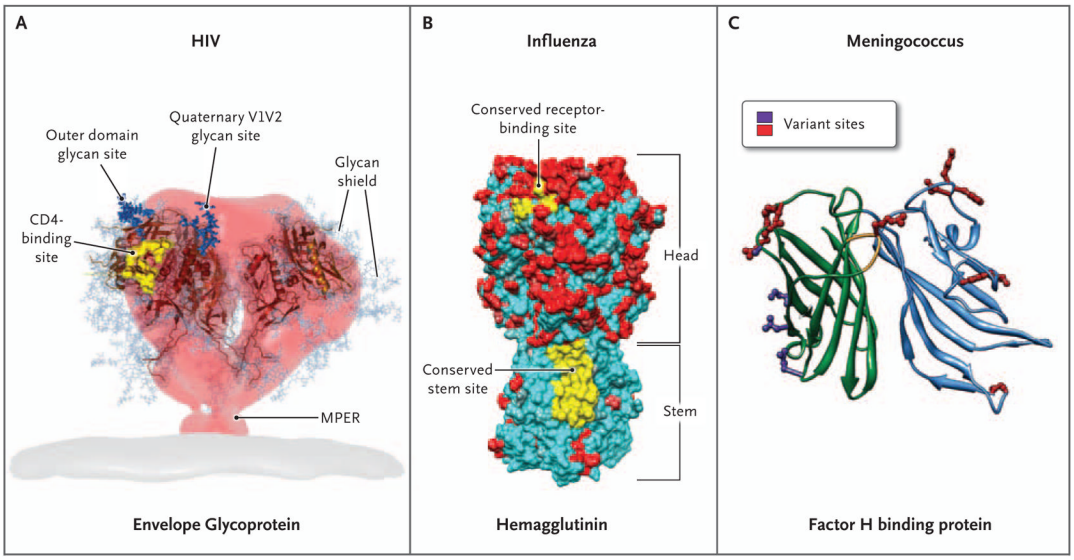

Figure 2. Structure of Viral or Bacterial Glycoproteins and Their Role in Host Invasion

A detailed knowledge of the mechanism by which viral glycoproteins mediate entry into host cells can now be applied to pathogens that once were not susceptible to vaccines, including human immunodeficiency virus (HIV) (Panel A, Protein Data Bank code 3JWD), influenza virus (Panel B, Protein Data Bank code 1RU7), and meningococcus (Panel C, adapted with permission from Scarselli et al.; Protein Data Bank code 2Y7S).[9–11] MPER denotes membrane proximal external region, and V1V2 variable regions 1 and 2. The Protein Data Bank is accessible at www.pdb.org.

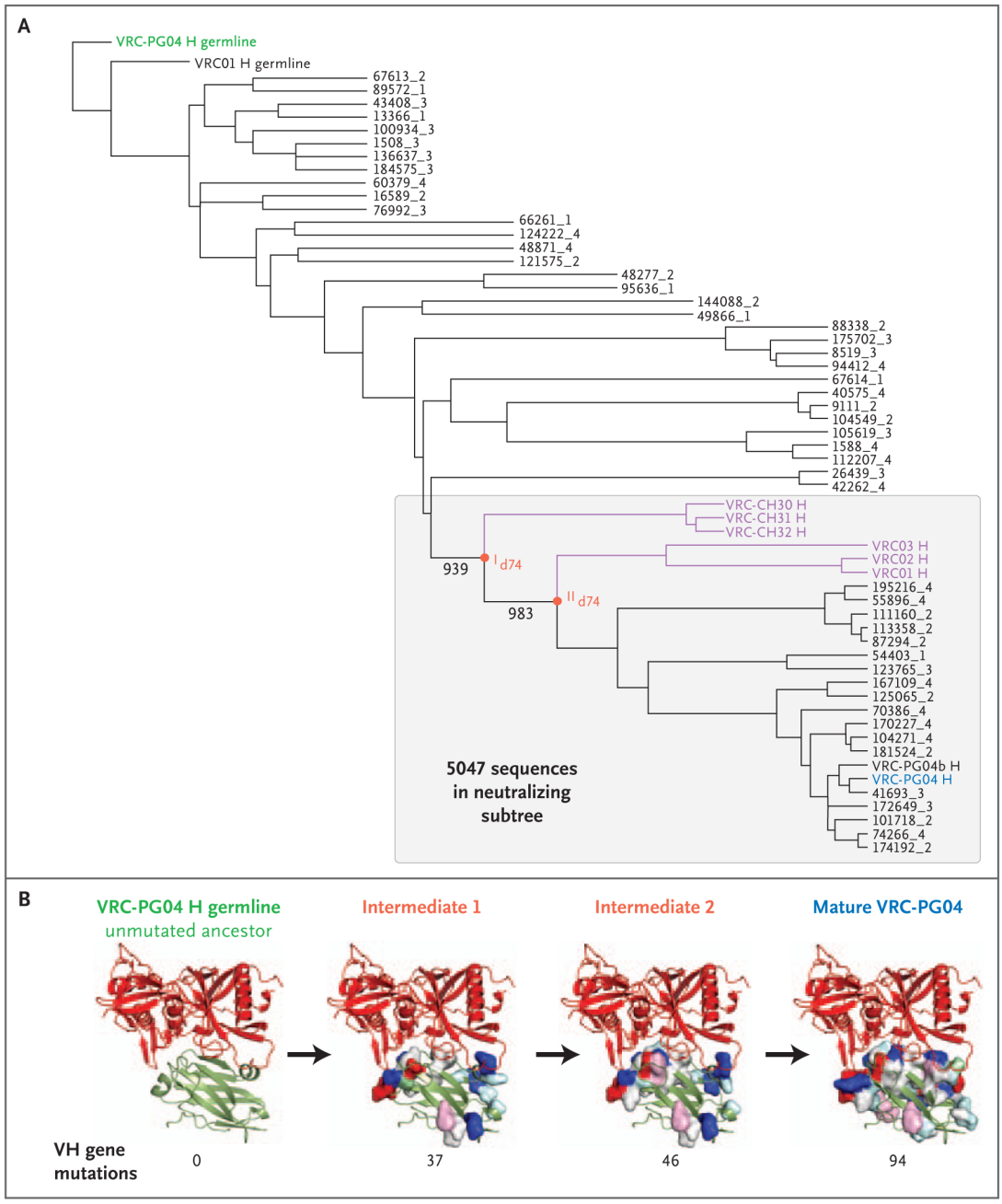

Figure 3. Molecular Evolution of a Successful Broadly Neutralizing Antibody

Deep sequencing (i.e., the ability to generate millions of independent sequences of a gene product) identifies critical intermediates for the evolution of broadly neutralizing antibodies and guides vaccine development. In Panel A, maximum-likelihood trees of heavy-chain sequences were derived from the IGHV1-2 gene that gives rise to a broadly neutralizing antibody, VRC01, in a representative patient, donor 74, as described previously.[23] The donor 74 tree is rooted in the putative reverted unmutated ancestor of the heavy chain of a specific broadly neutralizing CD4-binding site monoclonal antibody, VRC-PG04 (as shown in Panel B, Protein Data Bank code 3SE9). Sequences from other donors are included in the cross-donor phylogenetic analysis. Bars representing 0.1 changes per nucleotide site are

shown. Sequences within the shaded box include autologous VRC01-like heavy-chain sequences that neutralize HIV with good potency and breadth and are probably clonal relatives of VRC-PG04. Sequences highlighted in blue and purple represent broadly neutralizing antibodies isolated with structural probes.

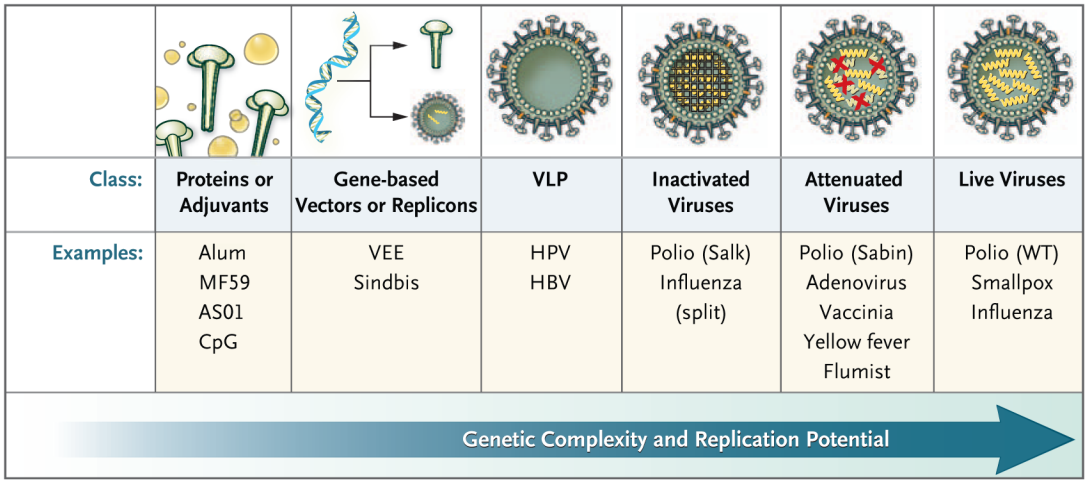

Figure 4. The Spectrum of Costimulation from Adjuvants to Viruses

A cellular and molecular understanding of dendritic-cell biology has facilitated improvements in vaccine-induced immune responses. Rather than generating responses through infection, immune stimulation can be achieved by increasingly complex modes of antigen presentation that range from introduction of selected proteins, with or without adjuvants, to gene-delivered immunogens, viruslike particles (VLP), structured arrays, or attenuated viruses. These approaches represent a spectrum of complexity and mimicry that elicits protective immunity without inflicting the adverse consequences of natural infection. HBV denotes hepatitis B virus, HPV human papillomavirus, VEE Venezuelan equine encephalitis, and WT wild type.

Table 1

Estimated Cumulative Number of Cases of Selected Infectious Diseases in the United States in the 20th Century before the Advent of a Vaccine, as Compared with Mortality after Utilization.*

Disease	Estimated Prevaccine Cases in 20th Century	Deaths in 2002
	number	
Smallpox	4.81 million	0
Poliomyelitis	1.63 million	0
Diphtheria	17.60 million	2
Haemophilus influenzae	2.00 million	22
Measles	5.03 million	36
Mumps	1.52 million	236
Pertussis	1.47 million	6632
Rubella	4.77 million	20
Tetanus	0.13 million	13

*Data are from the Centers for Disease Control and Prevention[3] and Roush and Murphy.[4]