

Why We Need Precision Vaccinology

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Keywords. antibodies; efficacy; epidemiology.

Vaccinology has had wonderful successes over the last 200 years since Edward Jenner first used animal poxvirus to prevent smallpox in humans [1]. Vaccines have been developed in 2 broad categories: live attenuated and killed inactivated, both yielding powerfully protective preventives. However, those successes have often come by chance after laborious and long development depending on best guesses and good fortune. Toward the end of the last century, methods for vaccine development evolved toward predictable techniques that allow for better design and more rapid development. One term for this is “precision vaccinology,” the subject of the articles in this supplement of *Clinical Infectious Diseases* [2].

Vaccine development initially and even now is focused on diseases that are difficult to treat and for which prevention is the best strategy. Although many endemic infections fall into this category, one must admit that epidemics of disease have often been the stimulus for vaccine development. The human species has been the host for innumerable endemic infections such as smallpox and malaria, but only some have caused devastating pandemics that threatened civilization. Many of those are listed in Table 1 and described in books [3]. Although in some cases a hundred years have passed between epidemics such that human memory had forgotten the prior ones, the fact is that humanity has been a fertile host for microbial outbreaks, and if anything, they are more frequent now than ever before thanks to greater human mobility and contact.

For most of the history of vaccinology, vaccines have consisted of killed organisms that caused a disease, or organisms weakened by being passaged in unnatural environments until they lost pathogenicity. It was the advent of molecular biology and genetic engineering that enabled us to create potent

vaccines with more specificity. Table 2 lists strategies for development of inactivated nonliving vaccines beyond simple killing. Capsular polysaccharides conjugated chemically to proteins become potent at preventing bacteria that rely on those polysaccharides to evade host defenses [4]. Analysis of proteins coded by bacterial genomes allows selection of important antibody-producing proteins [5]. Structural analysis enables selection of proteins that induce protective responses. A whole host of adjuvants that stimulate Toll-like receptors are now being used to replace simple aluminum salts [6]. Nucleic acids coding for important proteins, both messenger RNA and DNA, can now be used to synthesize proteins important for protection [7, 8].

New strategies to develop live vaccines are listed in Table 3. Reassortment of genes for viral proteins was used to develop a vaccine against rotavirus infantile diarrhea [9]. In addition, deleting genes from viruses to attenuate their virulence achieves rapid attenuation, as does recombining genes from virulent and attenuated organisms. Vectors such as adenovirus or vesicular stomatitis virus can carry genes from pathogens and express their protective proteins. More directly, sequences of nucleic acids that code for important antigens can be changed so that the living organism is attenuated and useful as a vaccine.

Despite the great success of vaccines in this century, typified by the high efficacy of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we must admit that important problems remain. For example, the efficacy of

Table 1. Epidemics of the Past

Date	Epidemic
430 BC	Plague of Athens
160 AD	Plague of Antonine
542 AD	Plague of Justinian
1340 AD	The Medieval Plague
1500 AD	Plague of the Incas
1665 AD	Great Plague of London
1793 AD	Yellow fever
1832 AD	Cholera
1918 AD	Influenza
20th–21st century	Ebola, HIV, swine flu, chikungunya, Zika, COVID-19

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus.

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Clinical Infectious Diseases® 2022;75(S1):S2–4

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Table 2. New Strategies for Inactivated Vaccine Discovery

Strategy
Protein-conjugated capsular polysaccharides
Reverse vaccinology
Antigen identification by transcriptomics and proteomics
Structural analysis
Development of new adjuvants (including cytokines)
DNA plasmids
mRNA and self-amplifying RNA
Abbreviation: mRNA, messenger RNA.

Table 3. New Strategies for Attenuated Vaccine Discovery

Strategy
Temperature-sensitive mutations and reassortment
Viral recombinants and deletion mutants
Codon de-optimization
Vectors that present genes from pathogens

Table 4. What Is New About Vaccination for Coronavirus Disease 2019

What Is New About Vaccination for Coronavirus Disease 2019
Desire of public for vaccination
Multiple strategies used for vaccine development
Financial support by governments
Importance of mutations, as in influenza
Multiple manufacturers, including in low- and middle-income countries

acellular pertussis vaccines wanes with time after vaccination of infants, influenza vaccines have only modest efficacy, and there are as yet no licensed vaccines against respiratory syncytial virus (RSV) or human immunodeficiency virus.

With respect to pertussis, replacement of chemically inactivated pertussis toxin with genetically inactivated pertussis toxin allows persistence of epitopes that induce higher efficacy [10]. Influenza vaccines may be improved by the addition of stalk antigens as well as the heads of the hemagglutinin molecules [11]. RSV vaccines for the elderly will certainly be improved by stabilizing the prefusion F antigen of the virus, whereas new mutated RSV strains may provide protection for infants [6, 12].

Other problems worth mentioning include the difficulty of developing a vaccine against herpesviruses including herpes simplex virus, human cytomegalovirus, and Epstein-Barr virus. The reasons for this include the cell association of the viruses and the importance of generating Fc effector functioning antibodies as well as neutralizing antibodies. On the other hand, vaccines against cancers induced by viruses are promising [13].

Table 5. Unsolved Problems in Vaccinology

Problem	Solution
Immune memory	More stimulus of Tfh cells Role of IL-7?
	Stronger induction of innate immunity by TLR agonists
Multiplicity of virulence antigens in complex pathogens	Antigenomics—analysis of natural immune responses
Multiple HLA types	Polyepitope vaccines
Conserved epitopes	Structural biology
Finding correlates of protection	Systems biology ^a
Immaturity and postmaturity of the immune system	Add cytokines or neutralize cytokines?
Mucosal immunization with nonreplicating antigens	Use nanoemulsions?
Adjuvants capable of selectively expanding cell types: dendritic, B, Th1, Th2, Th17, CD4 ⁺ , CD8 ⁺ , or Tregs	Use single or combined TLR ligands?
The difficulty to generate T-cell immunity without replicating vaccines	Adjuvants?

Abbreviations: HLA, human leukocyte antigen; IL-7, interleukin 7; Tfh, T follicular helper; TLR, Toll-like receptor; Tregs, regulatory T cells.

^aAnalysis of humoral and cellular immune responses.

Table 6. Some Features of the Future of Vaccinology

Feature
Influenza—vaccine addition of neuraminidase and stalk
RSV—structural analysis of antigens
Attenuation by mutation of genomes
Nanoparticles
Messenger and self-amplifying RNA
Vectors carrying vaccine antigens
Induction of Fc receptor antibodies
Vaccines for the elderly
Manufacture in developing countries

Abbreviation: RSV, respiratory syncytial virus.

The race to produce vaccines against SARS-CoV-2 illustrates the advances in vaccinology. Table 4 lists some of the factors that allowed rapid development and deployment of vaccines, which also provide hope for the future of vaccinology, despite the resistance to vaccination that has been problematic in certain less progressive areas of the United States. The features that allowed for rapid development of vaccines against the new virus include knowledge concerning the mechanism of attachment and entry of coronaviruses into human cells, the presence of the receptor-binding domain in the spike protein that is the chief inducer of neutralizing antibodies, and the evident correlation of neutralizing antibodies with efficacy [14]. In addition, the profound and effective response of the vaccine industry to the emergency has been striking and unprecedented.

However, numerous problems remain in the field of vaccinology, some of which are listed in [Table 5](#), together with possible solutions. Fortunately, the advance of science in this century has been striking, leading to optimism about the future. [Table 6](#) lists some of the favorable developments that lead to the hope that by the year 2100 vaccinology will be triumphant against both infectious and noninfectious diseases.

Notes

Supplement sponsorship. This supplement is sponsored by the *Precision Vaccines Program* of Boston Children's Hospital.

Potential conflicts of interest. S. A. P. serves as a consultant for Merck, Moderna, New Link, Novavax, Omvax, Takeda, X-Vax, NTx, Valneva, Vaxart, Sanofi, and GSK.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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