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# Clinical vaccine development

Vaccination is regarded as one of the biggest triumphs in the history of medicine. We are living in the most successful period of vaccine development. The accumulation of multidisciplinary knowledge and the investment of massive funding have enabled the development of vaccines against many infectious diseases as well as other diseases including malignant tumors. The paradigm of clinical vaccine evaluation and licensure has also been modernized based on scientific improvements and historical experience. However, there remain a number of hurdles to overcome. Continuous efforts are focused on increasing the efficacy and reducing the risks related to vaccine use. Cutting-edge knowledge about immunology and microbiology is being rapidly translated to vaccine development. Thus, physicians and others involved in the clinical development of vaccines should have sufficient understanding of the recent developmental trends in vaccination and the diseases of interest.

**Keywords:** Vaccines, Vaccination, Clinical trial, History

## Introduction

Infectious diseases caused by viruses have been the most challenging problem in human health. The diseases with high infectivity and mortality are particularly feared, and in the past, people have regarded such diseases as a disaster or a punishment [1]. However, improvements in identifying the etiology of viral infections and knowledge about microbiology, which were followed by the development of various vaccines, have enabled humankind to overcome the irrational fear of death. The invention of vaccination is regarded as one of the biggest triumphs in the history of medicine. Vaccination has saved millions of lives and its importance is still growing.

Although numerous efforts have focused on producing qualified and effective vaccines, there are insufficient barriers to protect populations from diseases that may cause epidemics or pandemics (e.g., the Ebola virus epidemic in 2014) [2-4]. Thus, researchers are trying to increase the numbers of diseases that can be prevented by vaccines and, by doing so, to expand the target populations that will receive the benefits of vaccination in the future. In addition, vaccine development strategies are being tailored to the particular economic and health requirements of specific countries. The products under development and the numbers and types of clinical trials are influenced directly by this trend. This is why physicians and others involved in vaccine development should be alert to the current paradigm.



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This review article briefly summarizes the past and present trends in clinical vaccine development. Its aim is to increase understanding about vaccine development by providing up-to-date information.

### History of Clinical Vaccine Development

The history of the development and application of ‘vaccine-like’ substances to humans started in ancient times. Hilleman [1] depicted this history in a concise diagram (Fig. 1). According to this diagrammatic outline, we are living in the modern era of vaccine development, which is more successful and productive than any other period in history. This progress has been dependent on the abundant financial support received (left column).

Using knowledge based on experience and observation, people in the 12th to 15th centuries practiced ‘variola’ [1,5], the first known method of human immunization. Powdered scabs or fluid from the pustules of a smallpox patient were inserted into superficial scratches made in the skin of the recipient. Many variations of this technique were used in China, the Middle East, and Africa, and they spread widely throughout Europe in the 17th century. The first scientific in-

vestigation of this technique was made by Edward Jenner in 1796 when he used cowpox virus rather than smallpox scabs in a human experiment based on doctrines of the enlightenment. This was the origin of the term ‘vaccine’ and the beginning of vaccinology [1,6].

Despite the historic achievement of Jenner, because of insufficient fundamental knowledge about microbiology, no new vaccines were developed for more than a century. In the late 19th century, heroic scientists such as Louis Pasteur, Robert Koch, Emil von Behring, and Paul Ehrlich discovered the basic principles and developed the experimental methodology of immunology and immunotherapy that led to the next stage of vaccinology [1]. Following their seminal investigations, many other studies were performed and led to improved regulations (e.g., The Biologics Control Act of 1902), which resulted in the development of valid live and/or attenuated vaccines. New vaccines against diseases including rabies, typhoid fever, diphtheria, shigellosis, tuberculosis, tetanus, and pertussis were developed by 1930 [1,7,8]. However, during this period, vaccine research was limited to the areas of public and/or military need (World War I) because of restricted funding resources.

In 1931, an important transition to vaccine mass produc-

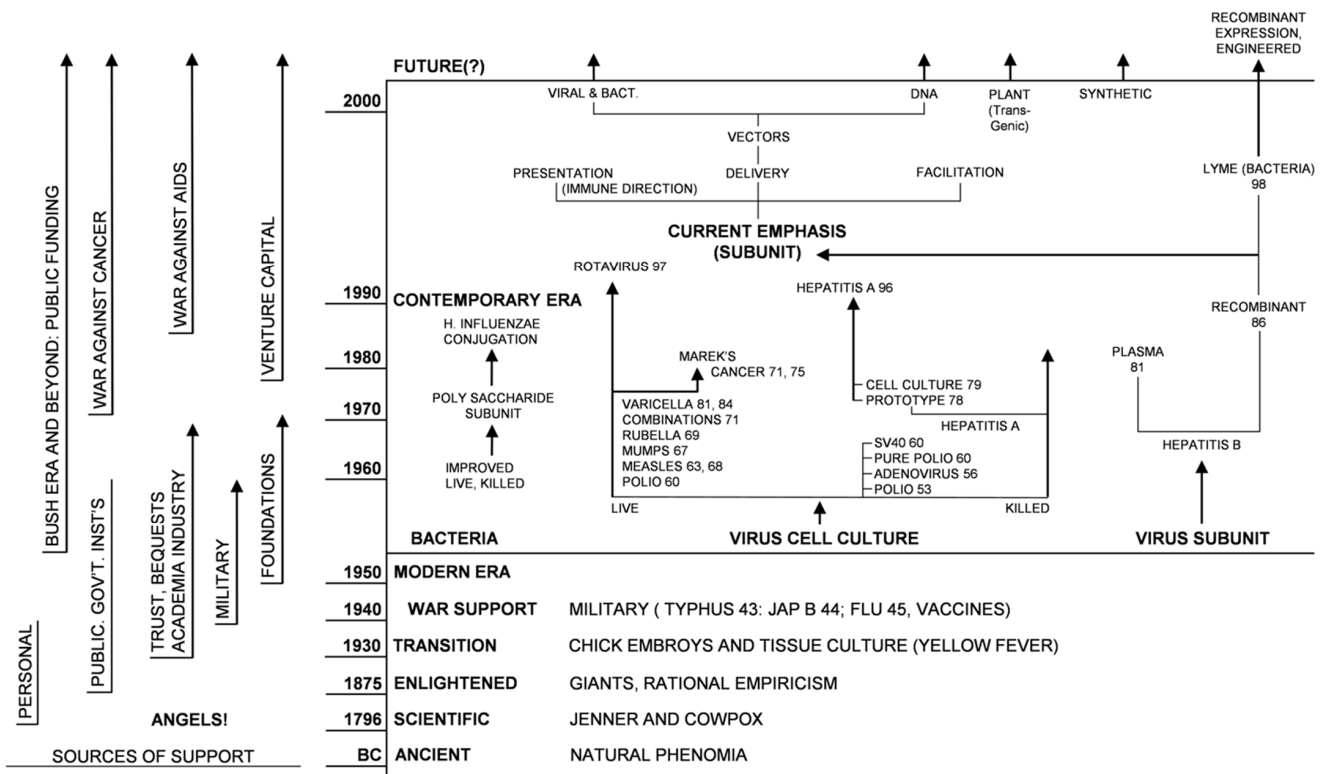


Fig. 1. Rise of vaccinology by Hilleman [1]. *H. influenzae*, *Haemophilus influenzae*.

## CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

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tion began with Good pasture's findings of viral growth in embryonated hens' eggs. Various manufacturing techniques were developed on this basis. In addition, the number of large-scale human tests with improved scientific validity increased during this period. The methodologies of randomization, blinding, and use of control groups helped increase the accuracy of the evaluation of the safety and effectiveness of vaccines. Between 1930 and 1950, and especially during World War II, military purpose remained a powerful motivation for vaccine development. Support from other bodies including public agencies and foundations (e.g., the World Health Organization [WHO] and the Rockefeller Institute) has arisen since then [1]. Vaccines against adenovirus, poliovirus, Japanese B encephalitis virus, and influenza virus were developed in this stage [9,10].

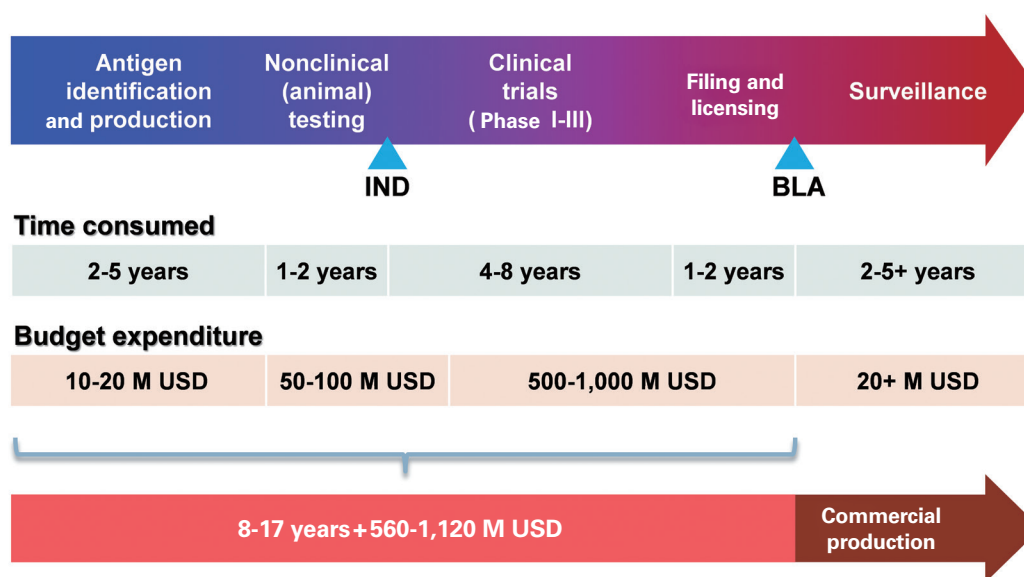
In the second half of the 20th century, defined by Hilleman [1] as the modern era, scientific improvements related to the screening and manufacturing of vaccine products enabled the development of new types of vaccines. Plotkin and Plotkin [11] regarded the same period as the 'golden age' of vaccine development. This age began with the development of three classical attenuated-virus vaccines against measles, mumps, and rubella (MMR) in the 1960s [12] followed by the varicella zoster virus vaccine and inactivated Japanese encephalitis virus vaccine in the 1970s. All of these vaccines involved cell culture techniques under controlled conditions for a certain purpose (i.e., attenuation) in their manufacturing processes. Inactivated whole hepatitis A virus and cell

culture-derived rabies viruses were also developed as vaccine products using similar methodology.

It was not until the 1980s that the conjugation of bacterial capsular polysaccharides to proteins was applied in a real-world setting, although it had been proposed in the 1930s by Avery and Goebel [13]. Thanks to this technology, bacterial vaccines against *Haemophilus influenzae* type b, meningococcus, and pneumococcus were introduced. Multivalent vaccines for various bacterial serotypes were also developed [14,15]. The development of recombinant viral vaccines using genetic engineering is another important step in the evolution of vaccinology. The first example of this type of vaccine was the vaccine against hepatitis B virus [16]. The human papillomavirus vaccine is another important example [17]. These kinds of vaccines brought dramatic improvement in vaccine safety, mitigating the risk of using purified inactivated antigens obtained from infected patients.

### Current Clinical Evaluation Vaccines

To meet society's need for safe and efficacious vaccines, the clinical vaccine development process has been refined for more than a century. Similar to that of chemical drugs, the clinical evaluation of a vaccine typically comprises three phases (Fig. 2). The entire process takes 10-15 years and requires a budget of about 1 billion US dollars. A vaccine-specific developmental plan should be clearly established to ensure the efficient and successful development before clinical evaluation.



**Fig. 2.** Current pathway of vaccine development. BLA, Biologic License Application; IND, investigational new drug; M USD, million United States dollars.

This includes the following contents: 1) identification of the target population (mostly healthy people with particular demographic characteristics) and their sociocultural factors; 2) risk assessment of the target disease and the vaccine itself; 3) understanding of the incidence of the target disease and environmental factors; 4) identification of the dose and route of administration; 5) plans to induce herd immunity; and 6) regulatory strategies. The general characteristics of clinical vaccine development compared with those of conventional drug development are summarized in Table 1.

Human studies of the acceptable safety and reactogenicity of a vaccine candidate are achieved in ‘Phase I’ clinical trials [18]. In this phase, safety and tolerability are evaluated at both the local and systemic levels as the primary endpoint. Dose-ranging and/or repeated-dose studies are often performed. Preliminary information on immunogenicity and efficacy may be collected [18,19]. These trials are often designed as randomized, double-blind, placebo-controlled, single-center studies. According to the characteristics of the product, either a crossover or parallel design may be chosen. The statistical analysis is generally descriptive and exploratory in nature because the trials involve only small numbers of participants (20-80), and thus sufficient information needed for confirmatory tests cannot be obtained [19]. In the ‘first-in-human’ setting, more attention should be given to live attenuated vaccines because the risks tend to be higher than those of killed vaccines [20].

In ‘Phase II’, the ‘proof-of-concept’ (PoC) of the vaccine product should be ensured. Clinical trials of this phase are

conducted to demonstrate the immunogenicity of the relevant active component(s) and the safety profile of a candidate vaccine within the target population and to define the optimal dose, initial schedule, and safety profile of a candidate vaccine [19]. These purposes are often achieved by separating clinical trials into ‘Phase IIA’ and ‘Phase IIB’. In designing these clinical trials, multiple variables associated with the host immune response are considered. Determinants of clinically applicable vaccine regimens are also included, such as the dose and number of doses, sequence/interval between doses, and route of administration. Vaccine efficacy may be evaluated using well-defined surrogate parameters. Most of these clinical trials include parallel group comparisons with placebo/active control groups. Prospective and confirmatory statistical analyses are performed, and the percentage of responders should be defined and described based on predefined criteria of an immune response (e.g., antibodies and/or cell-mediated immunity).

The final step in the clinical evaluation before product license is the ‘Phase III’ trial. This stage is intended to provide a pivotal conclusion needed for marketing approval, and the efficacy and safety of formulation(s) of the immunologically active component(s) must be assessed in the large-scale target population [18,21]. The clinical outcome is strongly recommended as a parameter for comparing efficacy (e.g., with placebo/active control groups). Therefore, serological data are usually collected from at least a subset of the immunized population at predefined intervals. The designs of Phase II and Phase III clinical trials are similar, but the size of a Phase

**Table 1.** The characteristics of clinical development of vaccines compared with those of clinical development of conventional drugs

	Vaccine	Drug
Database	15,000-100,000 subjects	~5,000 patients
Safety focus	Solicited short-term AEs; unsolicited AEs; long-term rare events	Unsolicited AEs (short- and long-term)
Acceptance of AE	Lower	Higher
Specific RA competence	WHO prequalification, FDA, EMA, few others	WHO less (or not) involved global registration
Manufacturing challenges	Biologics, clinical bridging trials (lot-to-lot comparison)	Well characterized, analytical comparisons
RA license issues	Manufacturing and clinical	Primarily clinical
Goals	Prevention of disease, death, sequelae	Treatment of disease, improved survival, QoL
Public health benefit	Herd effect in nonvaccinees	Individual effect
Proof of efficacy	Immunological surrogates Efficacy/effectiveness trials	Disease-specific surrogates Outcome: “dead or alive”
Serological tests	Reproducible results prerequisite for license, interlaboratory comparability lower	Not always required
Outcome studies	Often granted, cost saving	~\$50,000; cost per life-year gained as cost effectiveness threshold

AE, adverse event; RA, regulatory affairs; WHO, World Health Organization; FDA, United States Food and Drug Administration; EMA, European Medicines Agency; QoL, quality of life.

III trial is much larger. In consideration of the modern vaccination strategy—administration of multiple vaccines at the same time—interaction and/or interference with other vaccines are evaluated routinely. It is sometimes not possible to conduct a confirmatory study to determine the protective efficacy of products containing the same antigens that are already used commonly and/or whose target disease has a very low incidence [21].

The information obtained during the developmental processes mentioned above are summarized and filed for submission to regulatory authorities in support of an application for marketing approval. The WHO and each regulatory authority have their own guidelines to ensure the quality of the information provided [21,22]. As an example, the United States Food

and Drug Administration (FDA) calls the process ‘Biologics License Application’ (BLA). The multidisciplinary FDA review team reviews the efficacy and safety information needed to make a risk-benefit assessment and is advised by Vaccines and Related Biological Products Advisory Committee (VRBPAC). The appropriateness of label contents and the reliability of the manufacturing process are also reviewed [23]. Even though a vaccine may be licensed, the safety information provided for licensure is regarded as insufficient, because at that point, only a few thousand people have likely been exposed to the vaccine. Thus, many vaccines undergo postlicensure (‘Phase IV’) studies. In the United States, the Vaccine Adverse Event Reporting System (VAERS) was established to detect possible signals of adverse events associated with vaccines [24].

Age groups

<p><b>Pre-birth</b></p> <ul style="list-style-type: none"> <li>• Cytomegalovirus</li> <li>• Group B streptococcus</li> <li>• Hepatitis B virus</li> <li>• Meningococcus serogroups A, B, C, Y and W135</li> <li>• Pertussis</li> <li>• Respiratory syncytial virus</li> <li>• Tetanus</li> </ul>	<p><b>Infants and children</b></p> <ul style="list-style-type: none"> <li>• Diphtheria</li> <li>• Group A streptococcus</li> <li>• <i>H. Influenzae</i> type b</li> <li>• <i>Helicobacter pylori</i></li> <li>• Hepatitis A virus</li> <li>• Hepatitis B virus</li> <li>• Inactivated poliovirus vaccine</li> <li>• Influenza virus</li> <li>• Measles</li> <li>• Meningococcus serogroups A, B, C, Y and W135</li> <li>• Mumps</li> <li>• Pertussis</li> <li>• Pneumococcus</li> <li>• Respiratory syncytial virus</li> <li>• Rotavirus</li> <li>• Rubella</li> <li>• Tetanus</li> <li>• Vericella zoster virus</li> </ul>	<p><b>Adolescents</b></p> <ul style="list-style-type: none"> <li>• Cytomegalovirus</li> <li>• Diphtheria, tetanus acellular pertussis</li> <li>• Epstein-Barr virus</li> <li>• Herpes simplex virus</li> <li>• Human papiloma virus</li> <li>• Influenza virus</li> <li>• Meningococcus serogroups A, B, C, Y and W135</li> <li>• Parvovirus B19</li> </ul>	<p><b>Adults</b></p> <ul style="list-style-type: none"> <li>• Diphtheria</li> <li>• Hepatitis B virus</li> <li>• Influenza virus</li> <li>• Meningococcus serogroups A, B, C, Y and W135</li> <li>• Pertussis</li> <li>• Respiratory syncytial virus</li> <li>• Tetanus</li> </ul>	<p><b>Elderly</b></p> <p><b>Recurrent infections:</b></p> <ul style="list-style-type: none"> <li>• Group B streptococcus</li> <li>• Influenza virus</li> <li>• Meningococcus serogroups A, B, C, Y and W135</li> <li>• Pneumococcus</li> <li>• Respiratory syncytial virus</li> <li>• Varicella zoster virus</li> </ul> <p><b>Antibiotic resistance:</b></p> <ul style="list-style-type: none"> <li>• <i>Acinetobacter baumannii</i></li> <li>• <i>C. difficile</i></li> <li>• <i>Candida</i> spp.</li> <li>• Enterotoxigenic <i>E. coli</i></li> <li>• <i>Klebsiella pneumoniae</i></li> <li>• <i>P. aeruginosa</i></li> <li>• <i>S. aureus</i></li> </ul> <p><b>Cancer:</b></p> <ul style="list-style-type: none"> <li>• Breast cancer</li> <li>• Colorectal cancer</li> <li>• Prostate cancer</li> </ul>
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A

Special target groups

<p><b>Travelers</b></p> <ul style="list-style-type: none"> <li>• Cholera</li> <li>• Dengue</li> <li>• Enterotoxigenic <i>E. coli</i></li> <li>• Hepatitis A virus</li> <li>• Hepatitis B virus</li> <li>• Influenza virus</li> <li>• Japanese encephalitis virus</li> <li>• Malaria</li> <li>• Meningococcus serogroups A, B, C, Y, W135 and X</li> <li>• Paratyphoid fever</li> <li>• Rabies</li> <li>• <i>Shigella</i> spp.</li> <li>• Tick-borne encephalitis virus</li> <li>• Tuberculosis</li> <li>• Typhoid fever</li> <li>• Yellow fever</li> </ul>	<p><b>Patients with chronic diseases</b></p> <ul style="list-style-type: none"> <li>• Cytomegalovirus</li> <li>• Fungal infections</li> <li>• Influenza virus</li> <li>• <i>P. aeruginosa</i></li> <li>• Parainfluenza</li> <li>• Parvovirus B19</li> <li>• Respiratory syncytial virus</li> <li>• <i>S. aureus</i></li> <li>• Tuberculosis</li> </ul> <p style="text-align: center;">serogroup</p>	<p><b>Patients with HIV</b></p> <ul style="list-style-type: none"> <li>• Influenza virus</li> <li>• Pneumococcus</li> <li>• Pneumocytosis</li> <li>• Tuberculosis</li> </ul>	<p><b>Emerging infections</b></p> <ul style="list-style-type: none"> <li>• AIDS</li> <li>• Anthrax</li> <li>• Avian influenza</li> <li>• Cholera</li> <li>• Dengue</li> <li>• Diphtheria</li> <li>• Ebola virus disease</li> <li>• EV 71</li> <li>• Malaria</li> <li>• Meningococcus serogroup X</li> <li>• Plague</li> <li>• SARS</li> <li>• Smallpox</li> <li>• Swine influenza</li> <li>• Tuberculosis</li> <li>• West Nile</li> </ul>	<p><b>Poverty</b></p> <ul style="list-style-type: none"> <li>• Cholera</li> <li>• Dengue</li> <li>• Enterotoxigenic <i>E. coli</i></li> <li>• Hepatitis A virus</li> <li>• Hepatitis B virus</li> <li>• Hepatitis E virus</li> <li>• Influenza virus</li> <li>• Japanese encephalitis virus</li> <li>• Malaria</li> <li>• Meningococcus serogroups A, B, C, Y, W135 and X</li> <li>• Parasitic infections</li> <li>• Paratyphoid fever</li> <li>• Rabies</li> <li>• Rotavirus</li> <li>• <i>Salmonella</i> spp.</li> <li>• <i>Shigella</i> spp.</li> <li>• Tuberculosis</li> <li>• Typhoid fever</li> <li>• Yellow fever</li> </ul>
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B

**Fig. 3.** Target population for vaccines in the 21st century by Rappuoli et al. [25]. (A) The most important vaccines for each age group are reported. (B) Special target groups for vaccination in the 21st century. The most important vaccines for each target group are reported. The lists of vaccines reported are indicative and are not intended to be exhaustive. *C. difficile*, *Clostridium difficile*; *E. coli*, *Escherichia coli*; EV71, enterovirus 71; *H. influenzae*, *Haemophilus influenzae*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; AIDS, acquired immune deficiency syndrome; SARS, severe acute respiratory syndrome.



## Current Issues and Conclusion

One of the most important aspects of vaccinology in the 21st century is the extension of the target population by the development of new vaccines against emerging infections, tumors, and chronic diseases. Ultimately, the goal of modern vaccination may be expressed as to prevent or to cure as many diseases with vaccination as possible. Rappuoli et al. [25] presented this concept in a simple figure (Fig. 3). Meeting this challenge requires increasing both the number of vaccine clinical trials in nontraditional populations worldwide and the scientific expertise necessary for the successful development of new vaccines [26]. Many initiatives have been launched recently including the Decade of Vaccines, the Millennium Development Goals, and the US Institute of Medicine consensus study Identifying and Prioritizing New Preventive Vaccines for Development.

Another focus is to improve the efficacy and safety of vaccines even further beyond the overwhelming successes of

vaccines in the past several centuries. The most important keyword from the efficacy viewpoint is ‘adjuvant’ [25]. A number of vaccine products are licensed or under development in the form of a mixture of a vaccine and a certain adjuvant (Table 2). Most of the currently licensed adjuvanted vaccine products target influenza. The emphasis on the importance of adjuvants is gradually increasing with the aging of the population. Because they facilitate the immune response to vaccination in older people, many experts expect that adjuvants will be an essential component for widespread vaccine use in entire populations.

In the traditional paradigm, disease caused by vaccination has been a serious problem [27]. Rappuoli [28] has stressed the methodological approaches used to overcome the risks of vaccination in the 21st century (Table 3). In addition, thanks to improvements in genomic techniques, new vaccine-design methods, such as reverse vaccinology [29], have enabled the high-throughput screening of vaccine candidates with greater confidence in their safety profiles. The characteristics

**Table 2.** Vaccine adjuvants

Adjuvant name (year licensed)	Adjuvant class	Components	Vaccine (disease)
Adjuvant licensed for use in human vaccines			
Alum <sup>a)</sup> (1924)	Mineral salts	Aluminum phosphate or aluminum hydroxide	Various
MF59 (Novartis, 1997)	Oil-in-water emulsion	Squalene, polysorbate80 (Tween 80; ICI Americas), sorbitan trioleate (Span 85; Croda International)	Fluad (seasonal influenza), Focetria (pandemic influenza), Aflunov (pre-pandemic influenza)
AS03 (GlaxoSmithKline, 2009)	Oil-in-water emulsion	Squalene, Tween 80, $\alpha$ -tocopherol	Pandemrix (pandemic influenza), Prepandrix (pre-pandemic influenza)
Virosomes (Berna Biotech, 2000)	Liposomes	Lipids, hemagglutinin	Pandemrix (pandemic influenza), Prepandrix (pre-pandemic influenza)
AS04 (GlaxoSmithKline, 2005)	Alum-absorbed TLR4 agonist	Aluminum hydroxide, MPL	Fendrix (hepatitis B), Cervarix (human papilloma virus)
Vaccine adjuvants tested in humans but not licensed for use			
CpG 7909, CPG 1018	TLR9 agonist	CpG oligonucleotides alone or combined with alum/emulsions	-
Imidazoquinolines	TLR7 and TLR8 agonist	Small molecules	-
Poly (I:C)	TLR3 agonist	Double-stranded RNA analogues	-
Pam3Cys	TLR2 agonist	Lipopeptide	-
Flagellin	TRL5 agonist	Bacterial protein linked to agonist	-
Iscomatrix	Combination	Saponin, cholesterol, dipalmitoylphosphatidylcholine	-
AS01	Combination	Liposome, MPL, saponin (QS21)	-
AS02	Combination	Oil-in-water emulsion, MPL, saponin (QS21)	-
AF03	Oil-in-water emulsion	Squalene, Montane 80, Eumulgin B1 PH	-
CAF01	Combination	Liposome, DDA, TDB	-
IC31	Combination	Oligonucleotide, cationic, peptides	-

Adopted from the article by Rappuoli et al. [25].

TLR, Toll-like receptor; MPL, monophosphoryl lipid A; poly(I:C), polyinosinic-polycytidylic acid; Pam3Cys, tripalmitoyl-S-glycerol cysteine; AF03, adjuvant formulation 03; CAF01, cationic adjuvant formulation 01; DDA, dimethyldioctadecylammonium; TDB, trehalose dibehenate.

<sup>a)</sup>Adjuvants licensed in the United States.

**Table 3.** New strategies for improving vaccine safety

Screening for sequences homologous to proteins encoded by the human genome to remove sequences mimicking self-antigens
Immunohistochemistry to check cross-reactions with human tissues
Multiple cytokine induction to profile the Th1/Th2 immune response and the potential for autoimmunity
Availability of well-controlled cell lines to avoid the use of whole animals (smallpox) and primary monkey kidney cells (polio Sabin), which may induce autoimmunity or contain undefined viral/prion contaminants
Control of cell lines for prion proteins
Simulation of immune response data from different immunization regimens
Mathematical models of disease, biomarkers, immune response kinetics, efficacy, and safety
Mouse-human crossover studies to understand the role of Toll-like receptors (TLRs)
Animal and <i>in vitro</i> models to test disease enhancement (RSV, influenza, and measles)
Large Phase III and Phase IV studies to exclude statistically rare events

of vaccine recipients are also considered, and there is much focus on developing ways to personalize vaccination, which is termed ‘vaccinomics’ [30].

Without doubt, the quantity and quality of clinical vaccine development will improve greatly in the future. Simultaneously, the coverage of vaccines against diverse diseases will be broadened faster than ever. Integration of knowledge about microbiology and immunology, establishment of efficient vaccine development strategies, and streamlining of regulatory approval processes may facilitate this trend. Doing so will increase the chances that human society will experience the continued benefits of vaccination.

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