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Biotechnologies Applied in Biomedical Vaccines

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Abstract

Vaccination, the administration of an antigenic material (vaccine), is considered to be the most effective method for disease prevention and control. A vaccine usually contains an agent that resembles a diseases-causing pathogen and is often made from inactivated microbes, live attenuated microbes, its toxins, or part of surface antigens (subunit). However, the modern biotechnological tools and genomics have opened a new era to develop novel vaccines and many products are successfully marketing around the world. It is important to formulate and deliver these vaccines appropriately to maximize the potential advances in prevention, therapy, and vaccinology. New vaccines employing biotechnological innovations are helping us to change the way for illness prevention. The clinical application of vaccines will be diversified along with the development of biotechnologies. In modern society, the outbreak of many infectious diseases has decreased through vaccination, but the burden of noninfectious diseases is growing. The new biotechnologies may result in not only the appreciation of vaccines which are critical in inducing protection against an infectious disease but also the production of therapeutic vaccines which are effective for all diseases including infectious and noninfectious diseases.

Keywords: biotechnology, vaccine, genetic engineering, prevention, therapy

1. Introduction

A vaccine is a biological preparation that provides active acquired immunity to a particular pathogen. The agent stimulates the immune system to recognize itself as a foreign threat and thus destroys and remembers it, so that the immune system can easily destroy any of these pathogens when they later invade into the body. The following vaccine characteristics may be altered or enhanced by biotechnologies.

1.1. Type

Inactivated microbes, live attenuated microbes, toxoids, and subunits have been manufactured as vaccines and employed to trigger adaptive immune responses [1].

1.2. Mode of action

The process is an artificial induction of immunity with an effort to protect against infectious diseases by priming the immune system with an immunogen. Vaccination traditionally includes various ways of administration such as given by injection, oral, intranasal, and percutaneous administration.

1.3. Effectiveness

The efficacy of vaccines is dependent on a number of factors such as the disease itself, the strain of vaccine, the vaccination schedule, idiosyncratic response to vaccination, and assorted factors, such as ethnicity, age, or genetic predisposition.

1.4. Potency

The potency is critically correlated to vaccine quality and efficacy. Its assay methods are variable, including *in vivo* assay, such as mice challenge test, plaque reduction neutralization test (PRNT), and *in vitro* assay, such as enzyme-linked immunosorbent assay (ELISA).

1.5. Safety

Vaccines are one of the safest medical products, but they are sometimes risky. The safety should be evaluated in clinical phases and postmarket surveillance. Accurate information about the value of vaccines as well as their possible side effects helps people to make decisions about vaccination.

2. Biotechnology

Biotechnology is the technological application of biological organisms, systems, and processes to develop, make, or modify products for specific uses such as pharmaceuticals, crops, and livestock. It encompasses a wide range of procedures for modifying living organisms according to human purposes. Traditional methods are the employment of artificial selection and hybridization, but modern usage also includes genetic engineering as well as cell and tissue culture technologies. In this section, we review some biotechnologies applied for the development and production of vaccines.

2.1. Application

Biotechnology is mainly used in three ways as follows: separation of a pure antigen using a specific monoclonal antibody; synthesis of an antigen with the assistance of a cloned gene; and synthesis of peptides to be used as vaccines.

2.2. Approach

2.2.1. Reverse vaccinology

The basic idea of reverse vaccinology is that an entire pathogenic genome can be sequenced and screened by employing bioinformatics methods to explore genes. Functional genomics approaches, such as DNA microarrays, proteomics, and comparative genome analysis, are used for the identification of virulence factors and novel vaccine candidates. This new computational approach allows prediction of all antigens, independent of their abundance and immunogenicity during infection. The first attempt at reverse vaccinology began with *Meningococcus B* (MenB) vaccine. Moreover, it has been used on several other bacterial vaccines such as antibiotic-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae* [2].

Reverse vaccinology have changed the concepts and approaches for vaccine candidate selection and design. Genome investigation and selection of antigens provide a new way to study the pathogenesis mechanisms. The resulting lists of novel candidates which reveal new aspects of pathogenesis will promote the rational design of optimal vaccine antigens. Applying genomic approaches to study both hosts and pathogens will ultimately drive and guide next-generation vaccine design [3].

2.2.2. Recombinant subunit vaccination

The gene cloning is a powerful tool to synthesize protein materials to subunit vaccine by recombinant DNA techniques. Recombinant subunit vaccines are made from a fragment of protein (antigen) expressed in the laboratory using the viral DNA, for example, hepatitis B (HB) vaccine. The hepatitis B virus (HBV) gene that codes for the antigen is inserted into baker's yeast genome and then expresses the antigen protein. The antigen protein is harvested and purified to be used for the vaccine. This technique is also being used to explore a vaccine against hepatitis C [4].

Recombinant-DNA techniques can facilitate the development of new principles to design and produce subunit vaccines. The recombinant subunit vaccine can furthermore be adapted by gene-fusion technology, to be efficiently incorporated into immunopotentiating adjuvant systems. The recombinant strategies have become increasingly important to the passive vaccination strategy and use antibodies or antibody fragments to prevent infectious diseases [5].

2.2.3. Recombinant protein vaccination

Upon infection, a pathogen produces proteins to elicit an immune response from the infected body. The gene encoding such a protein is isolated from the causative organism and used to develop a recombinant DNA which is expressed in a heterologous expression system (e.g., bacterium, yeast, or insect). Recombinant protein vaccines, such as cholera vaccine, diphtheria toxoid, and tetanus toxoid, are composed of protein/toxin antigens that have either been produced in another host organism or purified from large amount of pathogens. The vaccinated persons produce antibodies to the protein/toxin antigen to protect themselves from diseases.

The baculovirus-insect cell expression system is also a recombinant protein manufacturing platform for the production of complex proteins. The technology is used for the mass production of various recombinant protein vaccines. The major advantage is that a universal “plug and play” process may be used to produce a variety of protein-based prophylactic and therapeutic vaccines for human uses [6].

2.2.4. Deoxyribonucleic acid (DNA) vaccination

DNA vaccination is a technique for protecting against diseases through the direct injection of genetically engineered DNA. The gene responsible for the immunogenic protein is cloned with a corresponding expression vector. This DNA will trigger an immune response and the individual is successfully vaccinated. DNA vaccines may have the ability to induce a wider range of immune response types over conventional vaccines.

Despite several DNA vaccines are available for veterinary uses, none of them is commercial for human uses. Research is being investigated using the approach for controlling infectious diseases and several cancers in humans. For instance, a synthetic consensus antispikes protein DNA vaccine induces protective immunity against Middle East respiratory syndrome (MERS) coronavirus in nonhuman primates [7]. The improved formulations and delivery methods can increase the uptake of vaccine plasmids by cells. The optimization of vaccine vectors and encoded antigens, and the adding of novel adjuvants potentially increase and direct the host immune responses. Therefore, current DNA vaccines may induce more potent, cellular, and humoral immune responses to be tested for both preventative and therapeutic uses [8].

2.2.5. Messenger ribonucleic acid (mRNA) vaccination

mRNA vaccines consist of mRNA, which is encoded by antigen genes of an infectious agent. When the mRNA is administered into host cells, it will translate protein antigens that elicit protective immunity against the infectious agent [9]. Vaccines based on mRNA may offer a solution as sequence-matched, clinical-grade material could allow quick responses to the emergence of pandemic microbe strains.

mRNA vaccines have an outstanding safety profile and the unmet genetic flexibility. mRNA vaccines can induce a balanced immune response comprising both cellular and humoral immunity. Compared with DNA vaccines, mRNA offers stronger safety advantages in which it harbors only the elements directly required for expression of the encoded protein and hardly interacts with the genome [10]. Because any protein can be encoded and expressed by mRNA without the need to adjust the production process, mRNA vaccines offer maximum flexibility with respect to vaccine production, and principally enable the development of prophylactic and therapeutic vaccines fighting against infections and cancers [10].

2.3. Advantages

- (1) Low risk for infection: Recombinant vaccines do not contain actual pathogens; only parts of the microbes (DNA, RNA, or protein) are used for making vaccines. Thus, recombinant

vaccines are safer than conventional vaccines and can be given to people with weakened immune systems.

- (2) Induction of more efficient immunity: Recombinant vaccines potentially induce both humoral and cellular immune responses to result in more effective vaccination.

2.4. Challenges

- (1) Complex vaccination schedules: The vaccines produced by biotechnologies are usually only parts of microbes (DNA, RNA, or protein); therefore, it is required to have multiple doses for maximum effectiveness either to produce sufficient initial immune responses or to boost responses that fade over time. To achieve full immunity, several doses must be given to induce additional “booster” shots for proper long-term immunity.
- (2) Economics: The research and development (R&D) of vaccines using biotechnologies is risky, costly, and time consuming. Most pharmaceutical firms and vaccine manufacturers have little incentive to develop vaccines based on biotechnologies because of limited revenue.

3. Products

Many products based on biotechnologies have been successfully marketing in many countries for years (Table 1).

3.1. Hepatitis B virus (HBV) vaccine: Recombivax HB®, Engerix-B®, Elovac B®, Genevac B®, and Shanvac B®

The vaccine is designed to prevent hepatitis B and currently produced with recombinant DNA techniques. It contains one of the viral envelope proteins-hepatitis B surface antigens (HBsAg) and produced in yeast cells, into which the genetic code for HBsAg has been inserted. The

Product	Recombivax HB®, Engerix B®, Elovac B®, Genevac B®, Shanvac B®	Rotarix®, RotaTeq®	Gardasil®, Cervarix®	Dengvaxia®	Bexsero®, Trumenba®
Preventive infection	HBV	Rotavirus	HPV	Dengue virus	<i>Neisseria meningitidis</i> group B strain
Indication	Hepatitis B	Gastroenteritis	Cervical cancer	Dengue	Meningitis
Vaccine type	Subunit vaccine	Live attenuated vaccine	Subunit vaccine	Live attenuated vaccine	Subunit vaccine
Administration	IM	Oral	IM	IM	IM

Human papilloma virus (HPV); hepatitis B virus (HBV); and intramuscular injection (IM).

Table 1. Vaccine products based on biotechnologies (recombinant DNA technology).

antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the adw subtype of HBsAg [11, 12].

3.2. Rotavirus vaccine: Rotarix® and RotaTeq®

This vaccine is designed to protect against rotavirus infections that cause vomiting and severe diarrhea in infants and children. It contains live attenuated viruses and should not be given to people who are clinically immunosuppressed. Rotarix® is a monovalent and indicated for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9). RotaTeq® is a pentavalent vaccine that contains five rotavirus strains produced by reassortment. Four reassortant rotaviruses express one of the outer capsid, VP7, proteins (serotypes G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein VP4 (type P7) from the bovine rotavirus parent strain [13, 14].

3.3. Human papilloma virus (HPV) vaccine: Gardasil® and Cervarix®

The vaccine is designed to prevent infection by certain types of HPV. HPV vaccines are subunit vaccines containing virus-like particles (VLPs) assembled from the major capsid protein (L1 protein) of HPV type 6, 11, 16, and 18 (Gardasil™) and type 16 and 18 (Cervarix™). Available vaccines protect against two or four types of HPV; however, all vaccines protect against at least HPV 16 and 18 that cause the greatest risk of cervical cancer. The L1 proteins of these HPV types (16 and 18) are separately produced using a recombinant baculovirus expression system and the insect cell line [15, 16].

3.4. Dengue vaccine: Dengvaxia® (CYD-TDV)

The vaccine is designed to induce an immune system to produce antibodies against four serotypes of dengue (DENV-1, 2, 3, and 4) and a live attenuated tetravalent chimeric vaccine using recombinant DNA technology by replacing the pre-membrane (PrM) and envelope (E) structural genes of the yellow fever live attenuated vaccine. For the vaccine, the virus is genetically engineered to include genes encoding for dengue proteins. Its production is based on a weakened combination of the yellow fever virus and each of the four virus serotypes [17–19].

3.5. Men B (*Neisseria meningitidis* group B strain) vaccine: Bexsero® and Trumenba®

The vaccine is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. The vaccine is manufactured using recombinant DNA technology (rDNA, component, adsorbed) and includes four antigenic proteins: Neisseria heparin binding antigen (NHBA), Neisserial adhesion A (NadA), Factor H binding protein (fHbp) and PorA to protect against the majority of circulating MenB strains [20].

4. Perspectives

In this section, we describe some trends for the development of vaccines using biotechnologies (Figure 1).

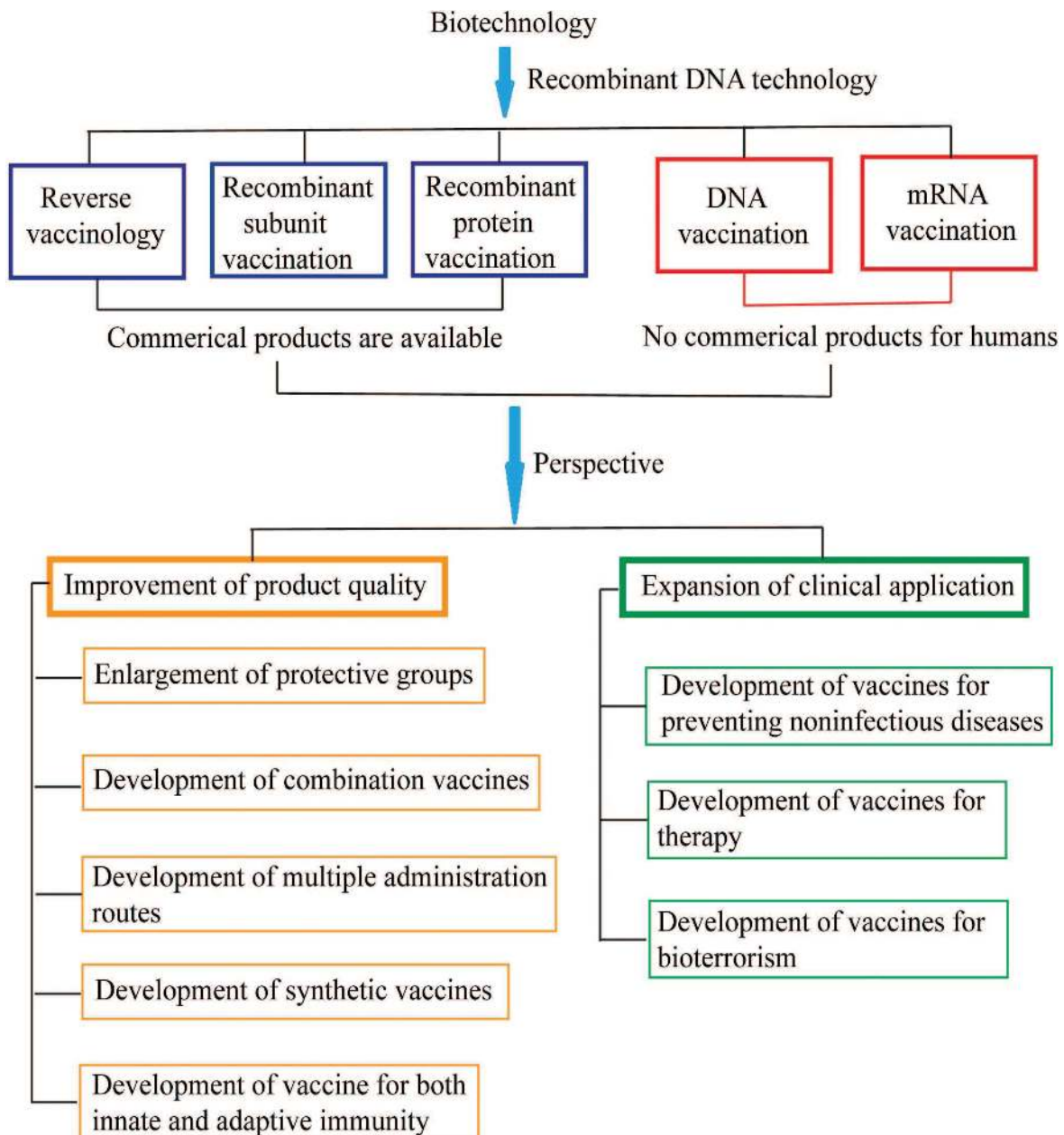


Figure 1. The perspectives of vaccine products based on biotechnologies.

4.1. Enlargement of protective groups

Most vaccines were focusing on infants and children, but adolescents and adults are gradually being targeted. During the course of their lives, adolescents and adults may need vaccination when they are hurt, sick, and pregnant or take a tour to some disease-endemic area. In addition, hospital patients, pregnant women, volunteer workers, individual with noninfectious diseases, and individual with chronic infections may need to prevent diseases necessarily than healthy persons; therefore, they will be the new target group for vaccination.

4.2. Development of combination vaccines

Combination vaccines include two or more vaccines that could be given individually or by combining them together into one shot. People get the same protection with fewer shots, compared with individual vaccines given separately. Fewer shots means less pain and stress for the people, especially for infants and children. For example, infants and children may only get one shot to protect him from three or even five diseases, instead of three or five individual shots. Diphtheria, tetanus, and pertussis (DTP) vaccine and measles, mumps and rubella (MMR) vaccine are two successful combination vaccines [21]. Also, combining vaccines make more infants and children get recommended vaccinations on schedule. Because scientists are developing more combination vaccines against more diseases, combination vaccines may become more common in the near future.

4.3. Development of multiple administration routes

Most of the vaccines are given by injection such as intramuscular (IM), subcutaneous (SC), and intradermal (ID) injection. Additionally, mouths and nostrils are two successful alternative routes for administration. For example, Sabin vaccine (OPV) and FluMist® are given by oral administration and intranasal spray, respectively. These two methods are more effective, inexpensive, painless, and convenient than injection. Microparticles introduced by biotechnologies have made it possible to have an inactive *Vibrio cholera* whole-cell vaccine that changes its administration route from injection to oral administration in mice [22]. Furthermore, more methods of administering vaccines through biotechnologies are being developed including patches, aerosol inhalation, microneedles, and even eating of genetically modified organisms (GMO).

4.4. Development of synthetic vaccines

Synthetic vaccines are composed mainly of synthetic peptides, polysaccharides, or antigens. They are usually considered to be safer than vaccines from bacterial cultures, because they are developed by reconstructing the outside structure of a microbe, which helps to prevent vaccine resistance. Diphtheria toxoid is the first synthetic vaccine which was created in 1982. Creating vaccines synthetically can expedite a specific vaccine production [23]. This is particularly important in the outbreak of a pandemic disease.

4.5. Development of vaccines for both innate and adaptive immunity

Conventional vaccines only induce adaptive immunity, but vaccines are being designed to stimulate both innate and adaptive immune responses. This can be accomplished by the addition of an appropriate adjuvant such as CpG oligonucleotides [24].

4.6. Development of vaccines for preventing noninfectious diseases

Conventional vaccines are only used to prevent infectious diseases in which active immunization is largely confined to infectious diseases. However, vaccines are being developed to prevent many noninfectious human diseases such as cancer, type I diabetes mellitus (T1DM),

Alzheimer disease and drug addiction, etc. Mostly efforts are being directed against cancers. It has been very successful in reducing the incidence of hepatoma and cervical cancer using of HBV and HPV vaccines for preventing virus infection. Several types of preventive cancer vaccines are being tried such as antigen vaccines, tumor cell vaccines, dendritic vaccines, DNA vaccines, and viral vector vaccines [25]. Tolerization to autoantigens is being attempted in T1DM; the administration of diabetes-specific autoantigens can elicit tolerance, which can prevent the destruction of β -cells [26]. Alzheimer disease may be controlled by immunization against amyloid [27]. It is known that drug addictions (e.g. cocaine) may be controllable by inducing antibodies that rapidly remove the drugs from the body [28]. Recent studies further reveal that the activation of Toll-like receptor 9 (TLR9) can improve the function of cocaine vaccines in the presence of TLR5 activation [29].

4.7. Development of vaccines for therapy

Vaccines are conventionally prophylactic, but vaccines are being developed to treat chronic virus infection and cancer.

- (1) Chronic virus infection: The induction of cellular immune response can suppress chronic virus infections such as HBV, hepatitis C virus (HCV), human immunodeficiency virus (HIV), and HPV [30].
- (2) Cancer: Some cancers are difficult to treat by conventional methods such as surgery, radiation, chemotherapy, and target therapy, but can be controlled by the immune responses triggered by cancer vaccines. However, the development of these therapeutic vaccines is extremely challenging. Fortunately, expanded studies and knowledge regarding the mechanisms how cancer cells escape the immune system may develop new means in modulating the immune responses to cancer; thus, potentially enhancing the effectiveness of therapeutic cancer vaccines.

4.8. Development of vaccines for bioterrorism

Bioterrorist attack is unpleasant and rare, but it may happen unexpectedly and often leads to serious events. It is needed to develop vaccines to defend against bioterrorism agents such as anthrax, plague, smallpox, and even severe acute respiratory syndromes (SARS). Such vaccines must provide protection against pathogens that might enter the body by a variety of routes including the oral and respiratory tract. They should be given by noninvasive routes and able to induce protective immunity rapidly. The design of improved vaccines is likely to rely on the genome information of bioterrorism agents that have either completed or have almost completed sequencing [31].

5. Discussion

The development of powerful biotechnological tools applied to genome-based approaches has virtually revolutionized vaccine development. The information of genome provides a list

of all the potential proteins from which it is possible for scientists to select some antigens or antigenic materials that are likely to be more effective vaccines [25]. Even if biotechnologies render many benefits for vaccine development, they are not always advantageous. The disadvantages include limited immunization to antigens, risk of affecting genes controlling cell growth, possibility of inducing antibody production against DNA, possibility of tolerance to the antigen produced, and potential for atypical processing of microbial proteins. In addition, it is a critical issue to formulate and deliver these vaccines appropriately to improve vaccine quality and expand their clinical application.

Vaccines dramatically reduce the incidence of serious infectious diseases and allow life expectancy of people to gradually increase. The persistent outbreak of many infectious diseases has decreased through vaccination; however, the burden of noninfectious diseases such as cancers, cardiovascular diseases, and diabetes mellitus has increased. This transformation of disease burden has indicated that the need for vaccines to treat or prevent noninfectious diseases is urgent. Both infectious and noninfectious diseases are now within the realm of vaccinology through the development of biotechnologies. Noninfectious disease vaccines also can be made by biotechnologies, but their target is human normal cells or abnormal cells, rather than pathogens or pathogen-infected cells. These vaccines present an interesting challenge for approving and evaluating under the same framework as traditional vaccines or that of other biologics, though they work by modulating the human immune system as traditional vaccines. Noninfectious disease vaccines have raised the question of whether the term “vaccine” is appropriate and some regulatory implications for this new category of drugs.

Despite vaccine development is rapid and clinical application is significantly expanded by biotechnologies, some infections, including HIV, HCV, SARS, MERS, Ebola virus, cytomegalovirus, and Zika virus, are under research and there are no effective vaccines available yet. Many vaccine candidates for these infections had been developed, but none had been approved for use in humans. The major difficulty for their clinical application is the lack of human clinical trials, the data insufficiency of for vaccine effectiveness, and the concern of vaccine safety. More funding, time, and research are needed for developing vaccines against recent emerging diseases such as MERS, Ebola virus, Zika virus infections, etc.

The perspectives for controlling diseases by vaccination are very promising along with the advancement of biotechnologies, but several problems are still hard to solve. First, vaccine supply is not sufficient even in the highly-developed countries, shortage of vaccines may occur due to regulatory pressures on production and the lack of qualified manufacturers. In the case of emergency, such as an influenza pandemic, it is difficult to estimate the demand of vaccine to satisfy the developing countries. Second, new vaccine discovery is very expensive and most of the manufacturers which do R&D have to pay the cost, but its revenue is limited. Some manufacturers may change their focusing products from vaccines to other medicinal products such as cell therapy products, gene therapy products, nanomedicines, and other products. Third, the requirement for vaccine safety is increasing, the evaluation of risk and benefit ratios become very crucial for the implementation of a vaccination program. But zero risk is almost impossible. It is quite difficult and controversial to obtain a balance between the need of public health and the regulatory impulse which guard against rare and theoretical risks.

6. Conclusion

Vaccination is the best approach to prevent infectious diseases. Vaccination is able to reduce the rates of mortality and morbidity from infection and results in herd immunity when some population has been vaccinated in some areas. Through vaccines distribution, some diseases are globally eradicated such as smallpox; some diseases are significantly controlled in much of the world such as polio, measles, and tetanus. However, there are many diseases uncontrolled yet by vaccination, and new diseases certainly appear through evolution, mutation, gene recombination, interspecies transfer, and environmental changes. Fortunately, we have many technologies to produce more novel vaccines to protect us. The previous studies have allowed us to understand the microbial pathogenesis and host immune responses which are correlated to the control of diseases by vaccination. Biotechnologies make it possible to further improve the quality of vaccines and expand the clinical application of vaccines significantly. More and more novel vaccine products based on biotechnologies are approved in the market around the world. Despite the great advances in biotechnologies, the perfect vaccine has not yet been developed. This vaccine would be temperature insensitive, multivalent and induce specific immunity against the protective antigens, would prevent and treat both diseases and possibly infections, would have long-term immunity without booster doses, free of adverse reactions, and administered without needles and the help of trained health workers. It is expectable to have such effective, cheap, and convenient vaccines for disease prevention and therapy provided that we endeavor to overcome the challenges in the production, distribution, and regulation of vaccines through biotechnologies.

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