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New achievements in vaccine development

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APSTRAKT

Vaccines have made a major contribution to global public health, including the eradication of one deadly disease, small pox, and the near eradication of another, poliomyelitis. In the future, vaccination will be expected to eliminate the remaining childhood infectious diseases.

Development of new, safe and effective adjuvants is also an important part of vaccine research. The new technologies minimize the risks associated with the new generation of vaccines. Research is also taking place into ways of making vaccines more thermostable, reducing the need for a cold chain for their storage and delivery. There are already needle- and pain-free vaccines that can be given as a nasal spray or taken orally, but researchers are coming close to releasing a new form of vaccine delivery called vaccine patches.

Vaccines can be used as a prevention of the development of a cancer or control of a cancer, but also to help to control chronic non-infectious diseases in adults.

A large number of very important vaccines such as vaccines against human papilloma virus, enterovirus 71, malaria, herpes zoster, meningococcal type B, as well as the first nasal vaccine and the first quadrivalent influenza vaccine etc. have been approved since 2000, and a great number of vaccines are currently under investigation.

Key words: vaccination, development, new indications

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Introduction

Vaccines have made a major contribution to global public health, including the eradication of one deadly disease, small pox, and the near eradication of another, poliomyelitis. Vaccination prevents between 2 and 3 million deaths every year and have the power not only to save, but also to transform lives – giving children a chance to grow up healthy, go to school, and improve their life prospects.[1,2]

However, vaccines could do much more. The Global Vaccine Action Plan has two great ambitions. The first is to deliver vaccination to all, because 1.5 million children still die every year due to diseases that can be prevented by the vaccines that human kind has developed. The second is to unleash vaccines' vast future potential - because their impressive history is just the foundation of greater achievements to come.[3]

The benefits of vaccination extend beyond prevention of specific diseases in individuals (Table 1.).[4]

Table 1. Benefits of vaccination

Disease control (eradication and elimination of the disease)
Control of mortality, morbidity and complications (for individuals and for society)
Mitigation of disease severity
Protection of the unvaccinated population (herd immunity, source drying)
Prevention of related diseases and cancer

Societal and other benefits such as health-care and other savings for society, preventing development of antibiotic resistance, extending life expectancy, safe travel and mobility, empowerment of women, protection against bioterrorism, promoting economic growth, enhancing equity, promoting peace.

In the future, vaccination is expected to eliminate the remaining childhood infectious diseases, and will address the health challenges of this century such as those associated with ageing, antibiotic resistance, emerging infectious diseases and poverty. However, in order for this to happen, we need to increase the public trust in vaccination so that vaccines can be perceived as the best insurance against most diseases across all ages.[5,6]

New approaches to vaccine development

The history of vaccination as a deliberate endeavor began in the laboratory of Louis Pasteur. Pasteur constructed the hypothesis that pathogens could be attenuated by exposure to environmental insults such as high temperature, oxygen and chemicals. His ensuing work on anthrax and rabies confirmed the hypothesis.[7,8] Until very recently, vaccines had been developed following the Pasteur example of inactivating and injecting the micro-organisms that are causing the diseases.[5]

Thanks to the technological revolution in the twenty-first century, genomics and the great development in immunology, nowadays it is possible to design vaccines efficient enough to prevent many of the diseases of modern society.[6,9] The initial priority of vaccine development has always been prophylaxis, but the development and evaluation of therapeutic vaccines, mainly for chronic infectious diseases and cancer, are gaining momentum.[10]

Vaccine development has become much more sophisticated with immunologists working closely with molecular biologists and chemical engineers to design and produce highly purified vaccines that are safe, consistently manufactured and effective.[9]

- DNA vaccines

Injection of DNA from a pathogen into a mammalian host can lead to incorporation of foreign DNA into the genome of host cells, with subsequent expression by host cells of the foreign antigen which then acts as a vaccine.[9]

- Vaccines based on antigens expressed in viral vectors

A number of viral vectors have been used to express a vaccine antigen, including modified vaccinia virus, fowl pox and human and chimpanzee adenoviruses. Viral vectored vaccines appear to work best when two different viral vectors are used in sequence or when a protein antigen is given after the vectored vaccine, an approach known as prime boost immunization. Prime boost immunization has been used successfully to develop malaria vaccines and is being used increasingly to develop vaccines against other pathogens.[9]

- Vaccines developed through a reverse vaccinology

Reverse vaccinology is a process by which selection of potential candidates for vaccine development is made at the genetic rather than at the protein level. Genes are selected on the basis of likelihood of leading to the expression of a protein that has characteristics desirable in a vaccine candidate antigen, for example, expression on the surface of a pathogen. This approach to vaccine development has been used to develop a Neisseria meningitidis serogroup B vaccine, and is being explored as a potential way of developing vaccines against a number of other organisms including S. pneumoniae.[9]

- Nanoparticle vaccines

The use of nanotechnology in vaccinology has been increasing exponentially in the past decade, leading to the birth of "nanovaccinology". In both prophylactic and therapeutic approaches, the use of nanoparticles in vaccine formulations does not only allow improved antigen stability and immunogenicity, but also targeted delivery and slow release. Types of nanoparticles that can be used in vaccines are: polymeric, inorganic and virus-like nanoparticles, liposomes, immunostimmulating complex, self-assembled proteins and emulsions.[11]

Development of new, safe and effective adjuvants is also an important part of vaccine research. Use of an adjuvant may convert a vaccine candidate antigen from one that gives too weak immune response to be useful to one that induces a strong enough response to provide clinical protection. The malaria vaccine RTS,S provides a good example of this. Powerful adjuvants have also been essential to the success of other vaccines, including therapeutic cancer vaccines. Use of an adjuvant may allow the dose of antigen in the vaccine to be reduced.[9,12,13]

A wide range of receptors are now recognized and the activation of which can lead to an enhanced helpful, or harmful, immune responses. Knowledge of the characteristics of each receptor and its activation pathway, and of the consequences of its activation, provides opportunities for modulating the immune response in a way of ensuring that an antigen induces a protective and not a harmful immune response.[9]

Safety of vaccines

The new technologies minimize the risks associated with the new generation of vaccines.

Highly purified components of known molecular entity, recombinant antigens, and polysaccharides conjugated to

purified proteins and new antigens discovered by genomics have allowed the development of a new generation of molecularly tailored vaccines that are well characterized and intrinsically safer than the crude preparations of the twentieth century. Live-attenuated vaccines that were derived by random passages and mutagenesis in the past have today been replaced by strains with molecularly designed attenuating mutations or by vectors designed to immunize but not replicate.

Finally, in the era of the technological revolution, we have plenty of new tools to predict safety risks of new vaccines. For instance, screening the vaccine candidates for sequence homology with the human genome allows identification and removal of those antigens that may have a risk of inducing autoimmunity that has so often been a problem in the past.[6] (Table 2.)

Table 2. New tools that will continue to increase vaccine safety

Immunohistochemistry to check cross reactions with human tissues
Multiple cytokine induction to profile the Th1/Th2 immune responses
Profile of cytokines induced by novel adjuvants and vaccines to predict the induction of expected immune response and the potential for autoimmunity
Availability of well-controlled cell lines to avoid the use of undefined non-controlled cell substrates for vaccine production such as brain extracts (rabies), whole animals (smallpox), primary monkey kidney cells (polio Sabin). These 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 cross-over studies for understanding the role of Toll-like receptors (TLRs)
Animal and in vitro models to test disease enhancement (RSV, influenza and measles)
Screening for sequences homologous to proteins encoded by the human genome to remove sequences mimicking self-antigens
Large phase III and phase IV studies to exclude statistically rare events

Administration of vaccines

Research is needed not only on the development of new vaccines but also on ways of delivering them. Development of non-reusable syringes for vaccination has cut down the risk of vaccination-related transmission of infection.[9]

Research is also taking place into ways of making vaccines more thermostable, reducing the need for a cold chain for their storage and delivery.[9]

While vaccines are very effective preventative care, shots can be painful. There are already needle-free and pain-free vaccines that can be given as a nasal spray (e.g. influenza vaccine) and taken orally, but researchers are coming close to releasing a new form of vaccine delivery called vaccine patches. These patches could be self-administered, distributed to a large number of people quickly, and helpful for kids (and adults) who have a fear of needles.[14]

Vaccines against non-infectious diseases

In the control of cancer, vaccines can be used as a prevention of the development of a cancer or control of a cancer once it has developed. Hepatitis B and HPV vaccines are preventive anti-cancer vaccines, regarding that HBV and HPV are important causes of liver and cervical cancer, respectively, both of which are very prevalent in the developing world. HPV is also implicated in the etiology of cancers of a number of other sites including the pharynx.[15]

Therapeutic anti-cancer vaccines have to enhance the naturally occurring host immune responses. They must be targeted at an antigen expressed by a particular cancer and thus may need to be specific for each patient. They also need to induce an immune response that overcomes self-tolerance mechanisms and the immunomodulating effect induced by cancer. Only one anti-cancer vaccine has been licensed so far, a vaccine against a prostate cancer which targets the enzyme prostatic acid phosphatase. Therapeutic anti-cancer vaccines, especially when they have to be individualized, are likely to remain very expensive and thus to have a limited impact on the overall global impact of cancer. In contrast, vaccines directed at the causes of these cancers have the potential to make a major contribution to improvements in global health.[15]

Vaccines can also be used to help to control chronic non-infectious diseases in adults. In the case of hypertension, some preliminary success has been achieved in lowering blood pressure by vaccination with the angiotensin II peptide presented in a nanovaccine on the basis of virus-like particles. Similar approaches are being explored in diabetes, nicotine addiction (as an important risk factor for cardiovascular disease as well as cancer), and in the management of other drug addictions.

New vaccines against infectious diseases

A large number of very important vaccines such as vaccines against human papilloma virus, enterovirus 71, malaria,

Ebola, meningococcal type B, as well as the first nasal vaccine and the first quadrivalent influenza vaccine etc. have been approved since 2000, and a great number of vaccines have been investigated.

Meningococcal B

Meningococcal disease is a severe infectious disease caused by Neisseria meningitidis (A, B, C, W-135 i Y).[16]

Persons belonging to risk groups (complement deficiency, asplenia, microbiologists being in contact with pathogen) have even 10 000 times higher risk of getting a disease and subsequent infection.[17] Considering that vaccines containing strains mentioned above do not protect against infection by serogroup B, which is normally the most common infection in Europe and the United States, studies still focus on finding vaccine against strain B.

In October 2014, the US Food and Drug Administration approved for the first time the use of a vaccine against the strain B that is given in 3 doses (0, 2, 6), under the code MenB-FHbp, and was evaluated in 7 clinical trials.[18] After that, in January 2015, MenB-4C was approved for usage in two doses (0,1), and licensed in 37 countries.[19] Both of the abovementioned have been approved for usage in people aged 10 to 25, but the US Advisory Committee on Immunization has expanded this application to all people older than 10 as well as to people belonging to certain risk groups.[20,21]

The latest information regarding the beginning of this vaccine application is that on September 1st, 2015 the Great Britain introduced MenB-4C into the regular vaccination schedule for toddlers/children older than 2 months and in 3 doses according to months of age (2, 4 and 12 months).[22]

Dengue

About 10 000 people in more than 100 countries die due to consequences of this disease.[23]

The most advanced candidate for the vaccine against this disease under the code CYD-TDV is progressing toward potential registration in 2016.[24]

After the administration of three doses over 12-month period, the safety and efficacy were monitored and analyzed in two pediatric studies, phase 3, in Latin America and Southeast Asia. Short-term safety profile of this vaccine is promising. So far, the most important benefit of the vaccinated persons has seen in a large reduction in the need for hospitalization of patients (67-80%). Efficacy data from clinical study, phase 3 have been updated (CYD14 and CYD15) as well as from the third and fourth year, phase 2b (CYD23/57).[25,26]

These results have shown that children aged 9-16 have the great benefit of vaccination and that is likely because CYD-DTV activates pan-serotype immunity in people who have already had a natural infection caused by this agent. Studies related to the vaccine against dengue CYD-TDV have provided a huge number of quality data on many aspects such as the nature of the disease, clinical epidemiology and nature of immunity.[27]

Herpes Zoster

Approximately 50% of persons who live to age 85 will experience Herpes Zoster, with the incidence rate still at rise.[28]

Live attenuated vaccine against Herpes Zoster, already licensed in the USA, decreases risk of Herpes Zoster for up to 70% at persons aged 50 and 59, for 64% for persons aged between 60 and 69, for 38% for persons older than 70.[29]

Lal and colleagues published the results of a phase 3 study of herpes zoster vaccine that consists of a single Zoster virus (VZV) glycoprotein on $AS01_B$ adjuvant system called HZ/su. This vaccine was tested in immune compromised volunteers who were older than 50 and it had a significant efficacy of 97.2%. Unlike live vaccine, vaccine efficiency did not decrease over the years after HZ/su administration; the effectiveness was 96.6% in persons aged 50-59, then 97.4% in persons aged 60-69 and 97.9% in those older than 70. HZ/su vaccine is administered in 2 doses, and live vaccine in one dose.

Adverse reaction rate was 2.2 higher in the group that received vaccine when compared to placebo group (66% vs. 30%), but the occurrence of adverse effects in the study of live vaccines administration was equal in both groups (25% in the vaccinated group and 24 % in the control group).[30]

Live vaccine that is currently in usage is contraindicated in patients with disorders of cellular immunity. Considering that the HZ/su vaccine contains a single viral protein, which means it cannot be replicated, its application will probably be safer in such patients.[31]

Ebola

Up to August 23rd, 2015, current Ebola epidemic led to 28 000 persons contracting the disease and 11,287 death cases.[32]

Several vaccine candidates are in the process of preclinical studies while the others are already in the stage of human trials.[33-35]

A vaccine against Ebola virus, based on an attenuated recombinant virus of vesicular stomatitis showed promising results in pre-clinical trials of 2 double-blind, placebo-controlled study of phase 1. The safety and immunogenicity

of the vaccine application were analyzed 28 days after the vaccination. There were no adverse effects registered while the immune response was found in all volunteers.[36]

The first results of phase 1 of clinical study were published in January 2015; they named 2 candidates for 2 different vaccines against Ebola: ChAd3-ZEBOV and VSV-EBOV showed their safety for usage. Phases 2 and 3 of clinical studies of candidates for vaccine VSV-EBOV currently take place in Guinea and Sierra Leone.

Using different vaccines for primo vaccination and revaccination, a strategy of two-dose regime of vaccine application was examined as well. This approach is known as heterologous primo-buster approach, and vaccines being tested in this regime are Ad26-EBOV and MVA-EBOV.[37]

Hepatitis E

Hepatitis E virus (HEV) is a very common cause of acute hepatitis in the world.[38-39]HEV virus infection is transmitted in two ways[40]: transmission through water and from animals to humans.[41-45]

Hepatitis E vaccine that was tested on 112 604 healthy volunteers provided a sustainable protection against this virus up to 4.5 years after the vaccination, regardless of whether they were previously healthy or had previously acquired natural immunity to HEV virus. There were no adverse reactions that would cause concern. The level of antibodies produced after vaccination declined faster in the first two years after the vaccination, after that more slowly, and their level was slightly higher after vaccination with 3 doses instead of 2.[46]

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Nova dostignuća u razvoju vakcina

SADRŽAJ

Vakcine su dale ogroman doprinos globalnom javnom zdravlju, uključujući iskorijenjivanje jedne smrtonosne bolesti, velikih boginja, i približavanje iskorijenjivanju druge bolesti, poliomijelitisa. Očekuje se da će vakcinacija u budućnosti eliminisati preostale dječije infektivne bolesti.
Razvoj novih, bezbjednih i efikasnih adjuvanata je, takođe, važan u istraživanju vakcina. Nove tehnologije su minimizirale rizike povezane sa novom generacijom vakcina. Istraživanja se, takođe, sprovode da bi se razvile termostabilnije vakcine, čime bi se smanjila potreba za hladnim lancem za čuvanje i transport vakcina. Već postoje vakcine koje se daju bez igle i bezbolno, kao što su vakcine za nazalnu i oralnu upotrebu, ali su istraživači vrlo blizu puštanja u upotrebu novog oblika primjene vakcine u obliku flastera za vakcinaciju sa mikroiglama.
Vakcine se mogu koristiti kao prevencija razvoja karcinoma ili za kontrolu karcinoma, ali mogu i da pomognu u kontroli hroničnih nezaraznih bolesti kod odraslih osoba.
Nakon 2000. godine za upotrebu je odobren niz vrlo značajnih vakcina kao što su vakcina protiv humanog papilomavirusa, enterovirusa 71, malarije, herpes zostera, meningokoka tip B, prva nazalna vakcina kao i prva četvorovalentna vakcina protiv influence itd., a veliki broj novih vakcina je u fazi ispitivanja.

Ključne riječi: vakcinacija, razvoj, nove indikacije