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Present and New Vaccines for Human Use

Sadašnja i nova humana cjepiva

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Summary

Vaccination is the least expensive and the most effective medical procedure. During the last 20 years, the percentage of vaccinated children has risen from 5 to 80 and this resulted in a 50 % reduction of morbidity and mortality rate from childrens' infectious diseases. Vaccines against measles, tetanus, pertussis, diphtheria, tuberculosis and poliomyelitis have been most important in achieving this result. These vaccines are very effective, with side effects of acceptable incidence and severity. Yet, their improvement is desirable, to make them more thermostabile (long-lasting transport), contain more immunogens (multiple protection with single application), applicable orally and as soon after birth as possible (early protection).

Research on vaccines for application to human (both children and adults) is directed toward improvement of existing vaccines and introduction of new ones. Because of these two goals, new technologies for preparation and application, new immunoadjuvants and new vaccines against: viruses, cancer, autoimmune diseases, parasites and AIDS are investigated. As an example, research in these three fields is described: protein carriers of vaccinal immunogens (synthetic, proteosomes, recombinant BCG), immunoadjuvants (nonionic polymers, saponins, monoclonal antibodies), and new ways of vaccine application (microencapsulation, attenuated viruses). It is concluded that new technologies provide opportunities for completely new approaches to preparation and administration of vaccines, at the same time enabling discoveries of new basic concepts of functioning of the immune system in men.

Sažetak

Primjena cjepiva najjeftiniji je i najdjelotvorniji medicinski zahvat. Tako je u svijetu, u posljednjih 20 godina, broj cijepljene djece porastao od 5 % na 80 %, što je prepolovilo oboljevanje i smrtnost od dječjih zaraznih bolesti. Riječ je o cjepivima protiv: ospica, tetanusa, hripavca, difterije, tuberkuloze i poliomijelitisa. Ta su cjepiva veoma djelotvorna, uz popratne pojave prihvatljive čestoće i opasnosti. Ipak se teži njihovu poboljšanju, tako da bi bila termostabilna (dugotrajan prijevoz), da bi sadržavala više antigena (višestruka zaštita jednom cijepljenju), da bi se primjenjivala na usta (ne injekcije) i neposredno nakon poroda (što ranija zaštita).

Istraživanja dječjih i ostalih humanih cjepiva svode se na pokušaje poboljšavanja postojećih i uvođenja novih. Radi tih dvaju ciljeva istražuju se nove tehnologije pripravljanja i načina primjene, novi imunoadjuvanti, te nova cjepiva protiv: virusa, raka, autoimunosnih bolesti, parazita te side (HIV-a). Kao primjer opisuju se najnovija istraživanja u ovim trima područjima: proteinskih nosača cjepivnih antigena (sintetski, proteosomi, rekombinantni BCG), imunoadjuvanata (nejonski polimeri, saponini, monoklonska antitijela) te novih načina primjene cjepiva (mikroinkapsulacije, atenuirani virusi). Zaključuje se da nove tehnologije omogućuju potpuno nove pristupe pripravi i primjeni cjepiva, ali se istodobno primjenom tih tehnologija otkrivaju nove osnovne spoznaje i zakonitosti djelovanja imunosnih sustava u ljudi.

Vaccines are the most cost-effective medical means known. The use of vaccines has been essential for prevention of a number of debilitating diseases. Several dangerous infectious diseases have been erradicated. The goal to erradicate polio, neonatal tetanus and measles has been set for this decade. Programs of vaccination were particularly effective since the World Health Organization had initiated the programs of Expanded Program of Immunization and the Children's Vaccine Initiative. Recently the Global Program for Vaccines has been organized, encompasing the previous programs *(1)*.

There are stil many unresolved problems with vaccines. The problems range from logistic to substantial, from the lack of money to buy the vaccines, lack of means to transport them properly to the target areas, attempts to educate people to understand the need for vaccination, to, for some diseases, shear lack of safe and effective vaccines.

Table 1. Estimated worldwide usage of vaccines in 1990[1]
Tablica 1. Procijenjen utrošak cjepiva u svijetu 1990. godine

Vaccine[2]	North America Europe, and Japan	UNICEF[3] PAHO and WHO	Other	Total
BCG	5	160	20	185
DTP	40	219	50	260
Hepatitis B	15		35	50
Influenza	75		10	85
Measles and combined (MMR)	15	131	30	165
Meningococcal	10	20	30	60
Polio (OPV, IPV)	60	450	190	700
Rabies	1	3	4	8
Total (%)	211 (14)	983 (63)	358 (23)	1552 (100)

[1] The data are from reference No. (*1*), p.67

[2] Expressed in millions of doses. Abbreviations: BCG = bacillus Calmette-Guerin; DTP = diphtheria, tetanus, pertussis; OPV = oral polio vaccine; IPV = inactivated polio vaccine; MMR = measles, mumps, rubella;

[3] UNICEF = United Nations International Children's Emergency Fund;
PAHO = Pan-American Health Organization

It has been estimated that the cost of vaccine itself is only 10 % of the total cost (labor 45, supplies 7, cold chain 8, social mobilization etc.).

World vaccine experts proposed a number of desirable features for future children's vaccines. They are to be: single dose, administered near birth, combined in novel ways, heat stable, effective against disease for which vaccines are unavailable, affordable.

In developing countries, where the vaccines are most needed, the mortalilty of children within the first five years of life is from: diarrhoeal disease 23 %, pneumonia 28 %, other 33 %, tetanus, tuberculosis, pertussis and measles together making about 15 %. The four last diesases are all vaccine preventable with the present vaccines *(1)*. In Table 1 are indicated the present vaccines which are in widespread use. It has to be taken into account that this is only a small part of the range of vaccines available.

To complete the information, in Table 2 are listed vaccines available in the USA (year 1993). This list is also an indicator of the range of vaccines available today.

One has to note, however, that not all of these vaccines are available in developing countries, where they are most needed. Also the range covers the diseases that are interesting for the USA. Many of the diseases of the developing countries do not have proper vaccines developed yet. Take as an example the vaccine against malaria. It is difficult to avoid mentioning ethical implications of these facts. Certainly, the research and development money does not follow the needs, but rather the sources. Just as an example, it is estimated that in 1993 about 35 % of the funds spent for vaccine-related research in an american institution will be spent for AIDS related research and only 5 % for tropical diseases *(1)*.

It is clear that in the field of vaccines, which has recently increased to the size that has justified organization of the International Society for Vaccines, and an entirely new scientific discipline vaccinology. The goals of the Society and professionals in vaccinology are to be wide, as wide as the list of problems, some of which are listed a few sentences above. Only one aspect of the problem will be elaborated to show what direction the research and development is taking to resolve these questions. The field is that of new technologies for vaccine preparation and application.

Again, it is impossible to mention here the whole range of innovative avenues in R&D in vaccinology. I shall take as an example a report on the International Conference Vaccines: New Technologies and Applications, held in 1993 in Washington, DC, USA *(3)*. Of the 10 conference sessions, the content of only three of them will be briefly described: New vaccine technologies, Vaccine adjuvants, New delivery technologies.

Under the heading of *new vaccine technologies* the subjects discussed included: novel protein carrier systems, anti-idiotype vaccines, proteosome carriers, recombinant BCG vaccines and antigen-specific vaccines. Among *new vaccine adjuvants* most attention was devoted to non-ionic block polymers, QS-21 (a saponin from the bark of the Quillaja saponaria tree), MF59 (an emulsion of squalene oil and surfactants Tween and Span), monoclonal antibody targeted immunogens, and monoclonal antibody stimulated clones of B cells. Finally several *new delivery technologies* were discussed. Controlled release by microencapsulation (lactide/glycolide polymers), glucan and protenoids. Within the framework of this heading also the use of highly attenuated viruses (e.g. vaccinia) were used to express relevant foreign genes.

I find appropriate to cite verbatim part of the Conclusion by R. Edelman *(3)*:

»One came away from this timely conference with the sense that vaccine research was alive and well and bursting with activity. Many unpublished concepts and approaches were presented, and discussions were open and free-ranging. Industry played a highly visible, even a predominant, role at the conference, but there were close ties to academia. Ideas and projects are being fuelled by an entrepreneurial spirit driven by powerful

Table 2. Vaccines, toxoids, immune globulins, and antitoxins available in the United States, 1993 *(1)*

Tablica 2. Cjepiva, toksoidi, imunoglobulini i antitoksini na tržištu u SAD *(1)*

Licensed vaccines and toxoids
Adenovirus vaccine, live oral, type 4
Adenovirus vaccine, live oral, type 7
Anthrax vaccine, adsorbed
BCG (bacillus Calmette Guerin vaccine)
Cholera vaccine
Diphtheria toxoid
Diphtheria toxoid, adsorbed
Diphtheria and tetanus toxoids, adsorbed (TD)
Diphtheria and tetanus toxoids and pertussis vaccine, adsorbed (DTP)
Diphtheria and tetanus toxoids and pertussis vaccine and *Haemophilus influenzae* type b
Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP)
Hepatitis B vaccine, plasma derived
Hepatitis B vaccine, recombinant
Haemophilus type b polysaccharide vaccine
Haemophilus b conjugate vaccine (HbCv)
Influenza virus vaccine
Japanese encephalitis virus vaccine inactivated
Measles virus vaccine live
Measles, mumps and rubella virus vaccine live (MMR)
Measles and mumps virus vaccine live
Measles and rubella virus vaccine live
Meningococcal polysaccharide vaccine A, C, Y, W135 combined
Mumps virus vaccine live
Pertussis vaccine
Pertussis vaccine, adsorbed
Poliovirus vaccine, inactivated
Polio vaccine live oral, trivalent
Plague vaccine
Pneumococcal vaccine, polyvalent
Rabies vaccine
Rabies vaccine adsorbed
Rubella vaccine
Rubella and mumps virus vaccine live
Smallpox vaccine
Tetanus toxoid
Tetanus toxoid adsorbed
Tetanus-diphtheria (Td)
Typhoid vaccine, live oral Ty21a
Yellow fever vaccine
Immune globulins and antitoxins
Botulism antitoxin
Cytomegalovirus immune globulin, intravenous
Diphtheria antitoxin
Hepatitis B immune globulin
Immune globulin
Pertussis immune globulin
Rabies immune globulin
Tetanus antitoxin
Tetanus immune globulin
Vaccinia immune globulin

Table 3. Selected groups of vaccines in development *(2)*

Tablica 3. Odabrane skupine cjepiva u razvoju *(2)*

Vaccines
Adenohepatitis B virus
Acellular pertussis
Diphtheria and tetanus toxoids and acellular pertussis
Diphtheria and tetanus toxoids and pertussis, *Haemophilus influenzae* type b
Diphtheria and tetanus toxoids and pertussis, *Haemophilus influenzae* type b, hepatitis B
Diphtheria and tetanus toxoids and pertussis, *Haemophilus influenzae* type b, hepatitis B, inactivated polio
Diphtheria and tetanus toxoids and pertussis, adsorbed, poliovirus (inactivated)
Hepatitis A
Herpes
Lyme disease (recombinant)
Measles, mumps, rubella, varicella
Meningococcal group B (outer membrane protein)
Pneumococcal conjugate (streptococcal conjugate, diphtheria toxoid and tetanus protein conjugates for otitis media and pneumonia)
Respiratory syncytial virus
Rhesus rotavirus
Sabin IPV (inactivated Sabin polio)
Salmonella, live attenuated
Streptococcal group B
Varivax varicella

profit-based market forces and the explosion in genetic engineering, protein, carbohydrate and nuclear acid chemistry, and immunology. The drive to bring products to market is spinning off fundamental information about complex biological processes at an accelerating rate. The future of vaccine research and development appears bright, and the public health will benefit....« So much for the optimistic outlook on vaccinology.

This brief review is concluded by a list of projects which are in various stages of vaccine development, but clearly indicate the status of the more immediate future in this field. The list is contained in Table 3.

More than giving a comprehensive and precise picture of the present state of the newly emerging field of vaccinology, this paper is an attempt, by selectively pointing out some parts of the total mosaic, to present the frame within which research and development of new vaccines is presently evolving.

References

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