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Contents

Summary

Better knowledge of the pathogenesis of infections and host responses, and progress in biotechnology, have paved the way for new vaccines. In spite of rapid progress with several vaccine candidates, overoptimism is, however, not warranted. There is usually several years' delay before the new vaccine from the laboratory is available in practice.

Acellular pertussis vaccine and rotavirus vaccine are examples of new vaccines that are currently being introduced; varicella, inactivated polio, and hepatitis B vaccines have been suggested for use in a new and more efficient way. In order to keep up high motivation among families and thus high vaccination coverage, more emphasis must be put on information about vaccines, their properties and proper use. Economic analyses are becoming more important in the decision to use new vaccines. Therefore, cost-benefit, cost-effectiveness and cost-utility analyses need to be conducted so that a basis can exist for determining a rational policy.

1. New Technologies and Old Bottlenecks

Large scale immunisation has led to the virtual elimination of several major infectious diseases of infancy, safely and with low cost. However, a long list of infections for which vaccines are either less than optimal or nonexistent is a continuous reminder of the need for new or improved vaccines. In addition, since even the best vaccines are not useful if they are not used, there is a need to develop and implement more efficient vaccination programmes.

Scientific advances have provided new tools for the development of vaccines. Sequencing of complete genomes of micro-organisms has led to the identification of new, potentially protective molecules. Improved protein purification and peptide

synthesis, monoclonal antibodies, and recombinant DNA techniques are currently widely used in the identification, isolation and engineering of such antigens. New adjuvants, formulations and delivery systems have been developed to induce optimal immune response. Recombinant DNA techniques also facilitate the construction of avirulent strains to be used as live vaccines, and the development of hybrid strains consisting of live vectors into which a gene of a protective antigen has been cloned. In genetic immunisation, non-replicative plasmids encoding a foreign protein are introduced directly into eucaryotic cells, in order to evoke an immune response to the protein.

Although it is important to recognise these new possibilities in vaccine development, overoptimism is not warranted. We still have gaps in basic knowledge of important host-microbe interactions, difficulties in the identification of protective epitopes, and problems in adjuvant development. Importantly, we must recognise that there will be a long delay before a new vaccine is available in child health centres and physicians' offices. It usually takes several years before scientific ideas have matured to prototype vaccines, and another, similar length of time before these vaccines have been proven safe and efficacious.

Clinical trials are laborious, but necessary, especially when no surrogates for protection have been identified. Since they are long-lasting and expensive, they seem to be the real bottlenecks in the development process. Another reality test for the candidate vaccines is the phase when public health authorities have to decide whether the new vaccine will be licensed and subsequently implemented in the vaccination programme. In addition to scientific and medical aspects, economic arguments are becoming increasingly important.

This review discusses childhood immunisation in the light of the literature published from 1995 to 1997. Given the broad topic and the limited space, the text unavoidably includes generalisations. For the details, the reader is encouraged to study the original publications.

2. New Vaccines for General Use

2.1 Acellular Pertussis Vaccines

Acellular pertussis vaccines consist of purified components of *Bordetella pertussis* bacteria. Antigens in the new vaccines include pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM2 and FIM3), in various amounts and combinations.

These new vaccines are clearly less reactogenic than the traditional whole-cell vaccines with which they have been compared. In a large multicentre trial, 20 to 33% of children had elevated temperature after administration of new diphtheria-tetanus-acellular pertussis vaccines (DTPa), compared with 60% in the traditional whole-cell vaccine (DTPw) group;[1] other general symptoms demonstrated the same trend. Comparison of local reactions at the injection site was similarly favourable to acellular vaccines: redness in 26 to 47% *vs* 73%, swelling in 16 to 34% *vs* 61% and pain in 2 to 11% *vs* 40%, respectively. In addition, severe reactions attributed to pertussis vaccinations occur less frequently with DTPa vaccines, although all different types of reactions have been reported.

The Swedish study of nearly 90 000 children reported lower relative risks after the DTPa vaccines than with DTPw (hypotonic-hyporesponsiveness episodes 0.47 to 0.85, high fever 0.19 to 0.41, and convulsions 0.15 to 0.46).[2] In 5 smaller studies the rates (events per 1000 vaccine doses) for high fever varied from 0.6 to 25.4 in the DTPa groups *vs* 0.0 to 45.7 in the DTPw groups *vs* 2.1 to 19.5 in the control groups receiving diphtheria-tetanus vaccine. Corresponding incidence rates for hypotonic-hyporesponsive episodes were 0.0 to 1.3 *vs* 0.0 to 8.4 *vs* 0.0 to 4.4, and for seizures 0.0 to 3.9 *vs* 1.6 to 2.9 *vs* 0.0 to 2.6, respectively.[3]

In the recent large, placebo-controlled efficacy trials of acellular pertussis vaccines, most investigators have used a strict definition for the end-point (at least 21 days of paroxysmal cough in connection with laboratory or epidemiological evidence of *B. pertussis* infection), thus measuring efficacy against the most severe forms of whooping cough.

Table I. Summary of recent prospective efficacy trials of acellular pertussis vaccines

Vaccine	Antigens	No. of doses	No. of vaccinees in DTPa arm	Efficacy (95% CI)		Reference
				DTPa vaccine	DTPw vaccine	
WL-4	PT, FHA, PRN, FIM2	4	4 273	82 (73-87)	91 (85-94)	3
AM-1[a]	PT	3	1 670	71 (63-78)	Not tested	4
AM-1	PT	3	1 670	75 (64-84)	Not tested	5
SKB-2[a]	PT, FHA	3	2 538	59 (51-66)	48 (37-58)	6
CLL-5[a]	PT, FHA, PRN, FIM2, FIM3	3	2 551	85 (81-89)	48 (37-58)	6
PM-2	PT, FHA	3	1 874	85 (66-93)	96 (86-99)	7
CLL-2	PT, FHA	4	12 710	82 (68-90)	96 (78-99)	8
SKB-3[a]	PT, FHA, PRN	3	4 481	84 (76-89)	36 (14-52)	9
CB-3[a]	PT, FHA, PRN	3	4 452	84 (76-90)	36 (14-52)	9
SKB-3	PT, FHA, PRN	3	22 503	89 (77-95)	96 (86-99)	10

a Blinded, prospective, controlled trials.

Abbreviations: AM = Amvax; CB = Chiron Biocine; CI= confidence interval; CLL = Connaught Laboratories Ltd.; DTPa = diphtheria-tetanus-acellular pertussis vaccine; DTPw = whole cell diphtheria-tetanus-pertussis vaccine; FHA = filamentous haemagglutinin; PM = Pasteur Merieux serums and vaccines; PRN = pertactin; PT = pertussis toxin; SKB = SmithKline Beecham; WL = Wyeth Lederle Vaccines and Pediatrics.

A summary of the main characteristics and results of these trials is given in table I. In the most recent trial, the best acellular vaccines and a good whole-cell vaccine were quite similar in efficacy (relative risk was 0.85 for the 5-component vaccine and 1.38 for the 3-component vaccine, compared with the DTPw).[2] In this study, the code for the 2-component vaccine group was opened prematurely, because the investigators anticipated poor protection on the basis of data from their previous study; the efficacy was indeed lower than in any other group.

The point estimates of the efficacy from different trials need to be compared with caution because of differences in study designs, vaccination regimens and follow-up methods.[11] These and other epidemiological conditions have a major impact on efficacy estimates. For example: the whole cell vaccine which demonstrated only 36 to 48% efficacy in randomised trials in epidemic conditions[6,9] was estimated to provide 90% protection in other study designs in nonepidemic regions of the US.[12] Interesting information can, however, be obtained when we compare different acellular vaccines with the whole-cell vaccines in the same trial, same vaccines in different trials, and the impact of additional antigens on the efficacy.

We can conclude from the data available that both whole-cell and acellular vaccines are able to provide protection against severe pertussis disease, although efficacy may vary with different vaccines. The best whole-cell vaccines and the best acellular vaccines are both highly efficacious, whereas the poorest vaccines in both groups offer an efficacy that scarcely justifies their use. The main advantage of the acellular vaccines is thus perhaps not their higher efficacy, but their favourable safety profile.

Several questions still deserve consideration. First, what is their efficacy against mild disease and asymptomatic infection, and can acellular vaccines curtail circulation of the bacteria? Preliminary evidence suggests that in this respect, multicomponent vaccines may be more efficacious than mono- or 2-component vaccines.

Secondly, do the acellular vaccines play a role in the immunisation of older children and adults? Data from immunogenicity studies suggest that acellular vaccines are tolerated well even by adults, but no studies have been performed where their efficacy has been measured in these age groups.

Thirdly, does the genetic variation of the antigenic structures of *B. pertussis* affect the protection achieved by pertussis vaccines? This question has

been raised in connection with recent outbreaks.[13,14] No answers are yet available.

2.2 Rotavirus Vaccines

Rotavirus infects nearly all children during the first years of life, and is a major cause of severe acute gastroenteritis in young children worldwide. Around 600 000 deaths of infants and children are caused annually by rotavirus. In industrialised countries, rotavirus accounts for approximately one-third of all hospitalisations due to gastroenteritis in children. Early clinical studies with live oral heterologous (bovine or rhesus) vaccines showed good efficacy against severe rotavirus gastroenteritis in Scandinavia and the US,[15,16] but the protection was insufficient in developing countries.[17] Therefore, these vaccines were not developed further. Similarly, human rotavirus (neonatal) strains also failed to induce protection against diarrhoeal illness when used as vaccines.[18]

Promising data of the safety and efficacy of a tetravalent rhesus-human reassortant rotavirus vaccine have been published recently. In this vaccine, the RNA segment encoding the VP7 surface protein has been replaced by the corresponding genome segment of a human rotavirus, so that the resulting reassortant expresses human rotavirus antigens on the surface of rhesus rotavirus. First studies in the US showed a protective efficacy of approximately 50% against all rotavirus disease, and of at least 80% against clinically significant diarrhoea.[19,20] The efficacy estimates in developing countries were lower, probably because a low dose of the vaccine was used. In Peru and Brazil the estimates for protection have been 20 to 35% for any rotavirus gastroenteritis and 50 to 60% for severe rotavirus gastroenteritis.[21,22]

Two recent studies add interesting information to the picture. Although adverse events reported after vaccinations are mild, they seem to be quite frequent – though less common than, for example, reactions after pertussis vaccines. Up to 15 to 29% of children have elevated rectal temperature, compared with 4 to 7% in the placebo group.[23,24] This is understandable, since with this reassortant vaccine induction of immunity is dependent on viral multiplication. The efficacy is higher among older children,[24] and higher still when the vaccination takes place close to the epidemic season.[23] Point estimates for the protection against rotavirus gastroenteritis were 66% in Finland and 48% in a poor population in Venezuela. In the case of severe rotavirus diarrhoea, the figures were 91 and 88%, respectively. These results encourage further testing, especially in developing countries with different dosages of the vaccine and different vaccination regimens.[25]

Despite the high incidence of rotavirus diarrhoea and good efficacy of the vaccine, rotavirus vaccines are not yet available in general vaccination programmes. Estimates for the economic impact of the disease and different immunisation programmes are requested by public health authorities before they make the decision to start wide scale use. Savings attributable to immunisation have recently been estimated to be $US11 to 20 per child in the US and Finland.[26,27] Whether this break-even cost is low or high remains to be judged by the parents, physicians and other decision-makers in healthcare. What may be needed to convince the decision-makers in developing countries is a large-scale demonstration project showing effectiveness, rather than efficacy, in addition to these economic calculations.[25]

3. New Ways to Use Old Vaccines

3.1 Varicella Vaccine

Varicella has significant health impact.[28] In the US alone, about 3.7 million cases of varicella are estimated to occur annually. Although most infections in otherwise healthy children are self-limited and free of complications, varicella can be a life-threatening infection, especially in immunocompromised patients. Live attenuated vaccine had already been developed in the 1970s, but its use has thus far been fairly limited outside Japan and Korea. Licensing of this vaccine and the strong recommendations for its wide use in the US in 1995[28]

have led to reconsideration of varicella vaccinations in several countries.

US recommendations urge immunisation of all children who have not been vaccinated previously and who lack a reliable history of varicella infection.[28] Serological testing before vaccination is not considered necessary, because most children who do not have a clinical history are susceptible, and the vaccine is well tolerated even by seropositive individuals. This policy was supported by a cost-effectiveness analysis of serotesting compared with presumptive vaccination.[29]

Varicella infections are also important from an economical viewpoint: with no vaccination, varicella was estimated to cause $US90 million in medical and $US439 million in work-loss costs each year in the US (1990 costings). A vaccination programme is expected to save more than $US5 for every dollar invested, if both work-loss and medical costs are included in the calculations.[30]

As the use of live varicella vaccine increases, the epidemiological features of the disease are expected to change. We might end up in a situation where an increasing part of the population is neither vaccinated nor exposed to wild-type virus, and thus susceptible to the spread of varicella epidemics.[31] Close surveillance of both the epidemiology of varicella-zoster infections and the immunity in different population groups is thus important.

3.2 Polio Vaccines

General immunisation with polio vaccines has led to the virtual elimination of poliomyelitis from large areas of the world, including the entire Western hemisphere. The disappearance of the wild poliovirus infection has induced risk-benefit considerations of polio immunisations in several countries. Although the risk of vaccine-associated poliomyelitis is low (approximately one case per 2.4 million doses), it has become the major factor in the discussion of the relative advantages of inactivated (IPV) or live (OPV) polio vaccines.[32,33]

The Advisory Committee on Immunisation Practices (ACIP) has given new recommendations for poliomyelitis prevention in the US.[34] Three alternative options are offered: sequential vaccination with IPV followed by OPV, OPV alone or IPV alone. The ACIP recommends a vaccination schedule of 2 doses of IPV (at 2 and 4 months) followed by 2 doses of OPV (at 12 to 18 months and 4 to 6 years) as the routine childhood vaccination. The option of OPV alone is preferred when the vaccination series is started after 6 months of age, or in children who are likely to travel to countries where polio is endemic. IPV is the only poliovirus vaccine recommended for immunocompromised individuals and their family contacts. Parents' perceptions of compliance with the vaccination visits, their attitudes towards injections and concerns about vaccine-associated poliomyelitis may also affect the choice of the vaccine.

Both IPV and OPV have their advantages and disadvantages, and each of the policies above has been followed successfully in the past.[32-34] OPV has been, to date, the preferred vaccine in most countries in the world. Some European countries, including Finland, Sweden, Norway, Iceland and The Netherlands, have relied exclusively on IPV in their routine poliovirus vaccinations. France and several provinces of Canada have joined this group. Denmark, Egypt and Israel have used the IPV followed by OPV schedule for years. Protection against the introduction of wild poliovirus in vaccinated populations and subsequent epidemics is not related to one vaccine or another, but rather to the existence of susceptible subpopulations. This stresses the importance of sustaining high immunisation coverage throughout the population, whatever the vaccination policy might be.

3.3 Hepatitis B Vaccine

Hepatitis B causes an estimated 4 million acute infections worldwide each year. The estimated number of long term carriers of hepatitis B virus is more than 350 million. Of these, approximately 25% will die from cirrhosis of the liver or primary liver cancer. In the face of this disease burden, and knowing that hepatitis B virus (HBV) vaccines are safe and efficacious, the WHO recommended in 1992 that all countries should integrate this vac-

cination into their national immunisation programmes by 1997. Following this recommendation, HBV vaccines have been implemented in universal childhood or adolescent immunisation programmes in 85 countries.[35,36]

Some Western European countries have remained unconvinced that the burden of disease warrants the expense of universal vaccination. However, strategies to immunise those at high risk have in most cases failed to control the disease. There is an increasing volume of epidemiological data showing that universal hepatitis B vaccination is cost effective even in countries with low endemicity, and that it will control hepatitis B.[36]

Examples of mass immunisation programmes in high endemic areas launched early and carried out successfully include programmes in Taiwan, Alaska and the Gambia. Follow-up of these immunisation programmes shows the long term efficacy of HBV vaccine, indicates a decrease in hepatitis B transmission, and suggests subsequent prevention of hepatocellular carcinoma.[37]

A district in the city of Taipei was studied in 1984 before the programme began and again after 10 years. The prevalence of surface antigen of hepatitis B virus (HBsAg) decreased from 9.8 to 1.3%. In those born after the start of the programme, HBsAg-positive rates decreased to 0.7%. The data also suggest that the subsequent prevention of hepatocellular carcinoma has begun to be seen in children in Taiwan. The annual incidence per 100 000 children between the ages of 6 and 14 varied between 4.5 and 7.1 in the years 1981 to 1991, but was reduced to 2.4 per 100 000 by 1993.[37]

The programme in Alaska also shows that mass immunisation of an endemic population can reduce the transmission of HBV, and that screening carriers leads to early detection of disease. Surveillance since 1981 shows that no one who responded to the vaccine later developed acute icteric hepatitis or became a long term carrier, indicating that protection lasts longer than 10 years. Despite the fact that antibody levels drop off rapidly, the protection persists. Screening carriers has also detected hepatocellular carcinoma at an early enough stage to significantly decrease mortality.[38]

3.4 Combined Vaccines

In recent years *Haemophilus influenzae* type b (Hib) conjugate and HBV vaccines have been introduced in several countries, and the use of IPV is also likely to be increasing. Since these vaccines are usually recommended at the same time as DTP, it is natural that their suitability for combination administration has been tested. In addition to the obvious benefits to the vaccinee (fewer injections and vaccination visits), combined vaccines are expected to lead to simplified vaccination regimens and increased compliance with the recommended programme.[39] Furthermore, combinations may lead to major cost savings. Hadler[40] estimated that the US vaccination programme could save up to $US13 to 335 million per birth cohort under ideal circumstances with proper use of combined vaccines (1992 costings).

The new combined vaccines are safe, sufficiently immunogenic, and protective. Although final antibody concentrations after primary immunisation with some combined vaccines have been slightly lower than with separately administered vaccines, this interference has not been considered clinically significant.[41,42] In the DTPa combinations, the interference seems to be stronger.[43,44] However, the most affected Hib antibody concentrations after the primary vaccination series exceed the concentrations that have been considered protective, and preliminary analysis indicates induction of immunological memory. It thus seems apparent that children are protected against invasive Hib disease. Interference is not a problem with combined vaccines containing DTPa and IPV or HBV.[45-47] Success in the development of these combined vaccines will certainly facilitate the implementation of acellular pertussis vaccines, and it most probably also accelerates the movement towards increased use of IPV and HBV in vaccination programmes.

The live, attenuated combination vaccine of measles, mumps, rubella and varicella is well tol-

erated and immunogenic, but here too interference between components has been a problem. Although more than 95% of vaccinees seroconvert for all 4 viruses, the level of antibody titre to varicella is significantly lower in those receiving the combined vaccine than in those who received varicella and measles-mumps-rubella vaccines in separate syringes.[48]

4. The Need for Health Promotion and Economic Analyses

The vaccination programmes of the WHO have led to one of the greatest public health achievements of the past few decades, rapidly increasing the coverage of childhood vaccinations in the developing world. Almost as big a public health achievement has been the maintenance of high vaccination coverage in other parts of the world. Most parents living in industrialised countries in the 1990s have not seen diphtheria, tetanus or tuberculosis. In some countries even measles, mumps and rubella have been rarities since the youngest of the present-day parents were children themselves. Therefore, parents have to rely on the information about the need for vaccines that they receive from healthcare providers. While health promotion thus far has been successful, it needs to remain a high priority in vaccination policies. In the future, more emphasis must be put on information about vaccines, their properties and proper use.

Economic analyses are becoming more important in the decision to use new vaccines. Decision-makers need to compare the value to society of programmes with different impacts, such as health programmes (immunisation programmes, etc.) with non–health programmes (e.g. education programmes, legislation to increase usage of safety belts in automobiles, etc). Inside the health sector, immunisation programmes compete for resources from many other preventive or therapeutic programmes. From decision-makers' perspective, vaccinations can be seen as an expense in the present, and their benefits will – or will not – occur in the future. Therefore, cost-benefit, cost-effectiveness and cost-utility analyses need to be conducted so that a basis for rational vaccination policies exists.

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