World Journal of Microbiology and Biotechnology 7, 105–109

## Papers presented at the IUMS Eighth International Congress of Virology, Berlin, Germany, 24–31 August 1990

# The ideal vaccine

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**The ideal vaccine is discussed under three headings. 1. The major requirements of the vaccine. This includes primarily safety and efficacy and a number of other desirable features if the vaccine is to control a disease of global importance. These include cost, easy administration (e.g. orally), thermal stability, multivalency and long-lived immunity. 2. The nature and persistence of the immune responses which, as judged by model systems, are probably generated by the most effective viral vaccines in current human usage. 3. Approaches for developing future 'simplified' vaccines with similar levels of safety and efficacy so that these objectives are achieved.**

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This paper was presented at the IUMS Symposium on New Developments in Diagnosis and Control of Infectious Diseases held in conjunction with the Eighth International Congress of Virology, Berlin, Germany, 24–31 August 1990.



The bicentenary of the dramatic demonstration in 1796 by Edward Jenner that prior inoculation of pox virus-infected material from cows to a human protected against the occurrence of disease following the subsequent exposure to the smallpox virus is close at hand. Now that the first vaccine made using recombinant DNA technology is licensed for human use and others will shortly follow, it is fitting that this meeting should discuss a series of basic questions about vaccines. One of these is—what are the properties of the ideal vaccine? If any practical benefit is to be derived from the answer to this question, two additional questions should be asked and answered according to our current understanding—What critical immune responses are generated by such a vaccine? and What are the most effective ways for vaccines of the future to induce these responses? This paper summarizes answers to these three questions.

## The Ideal Vaccine

There are two sets of requirements. The primary requirements are two-fold:

1. The vaccine should be safe, even in immunocompromised people. No current vaccine is completely safe but a mortality rate greater than $1/10^6$ would not be acceptable in the great majority of countries. The level of morbidity might vary according to the perceived disease impact in the population, but optimally, there should be no significant long-term sequelae. As far as immunocompromised recipients are concerned, the main danger is from vaccines containing an infectious agent. Recent experiments in immunocompromised animals gives rise to the hope that inclusion of genes coding for selected T cell growth factors in a recombinant vector may afford substantial protection (Flexner *et al.* 1987; Ramshaw *et al.* 1987).
2. The second requirement is that the vaccine should be highly effective and optimally induce 'sterilizing' immunity, i.e. vaccination results in the complete prevention of infection by a subsequent challenge dose of the wild-type organism. Whether this is ever achieved by a current vaccine is unknown. Such a requirement is particularly desirable in the case of retroviruses because integration of viral DNA into the cell genome during viral replication results in a cell potentially infected 'for life'—a situation to be avoided if possible.

In other situations, and in immunocompetent hosts, a vaccine may be optimally effective if vaccination reduces a subsequent infectious agent challenge load by say, 99.9%, so that the host's own immune system can comfortably cope with the remaining infectious agent. The vaccinee thus may benefit from the immune responses to both the vaccine and to a reduced wild-type infection.

Many vaccines in use today are to control diseases of global importance and almost all serious infectious diseases for which there are currently no vaccines are also in this category. There are a number of secondary requirements for an ideal vaccine against such infections. They include the following requirements.

1. Cost. To be included in the WHO Expanded Programme for Immunization, a vaccine should cost less than 50 cents/dose. The six childhood vaccines at present in the global Programme are supplied through UNICEF for a total of about 30 cents/schedule of administrations! This is much less expensive than the same vaccines provided in many National Programmes and gives some indication of the advantages of bulk purchasing.
2. Many vaccines are administered parenterally which adds to the total cost because of the need for skilled personnel. Administration via mucosal surfaces, and preferably orally, offers many advantages for vaccine delivery.
3. Particularly for use in tropical countries, the ideal vaccine should have a high thermal stability, thus obviating the need for expensive cold chains.
4. To save further on administration costs, a single vaccine might be multivalent, i.e. protect against several locally important infectious diseases. Sometimes, several vaccines may be administered as a mixture, e.g. DPT. The development of live recombinant vectors, such as vaccinia virus and Salmonella, which may include genes coding for many antigens, allows this possibility to be exploited in the future (Ada 1989).
5. Long-lived immunity. Some attenuated live viral vaccines give long-lived immunity after a single or two doses, e.g. vaccinia, measles viral vaccines. Generally, most non-infectious vaccines require a course of administrations with adjuvant to achieve comparable results. There is currently extensive ongoing research to explore ways for reducing the number of administrations, such as the use of controlled release preparations.

## The Nature of Protective Immune Responses

The efficacy of a vaccine depends primarily upon the nature and persistence of the induced immune response. Other than the role of antibodies in neutralization of viral infectivity (an *in vitro* assay), very little is known about the involvement of other immune responses following vaccine administration or natural infection of humans. A more complete understanding has come from the study of model viral–host systems, such as the murine influenza model (Ada & Jones 1986). Four stages are readily identified (Ada 1989) and are given below.

*1 Prevention of Infection*

As measured in an infectivity neutralization assay or by adoptive transfer, an antibody which recognizes particular epitopes on often a single surface antigen (e.g. the haemagglutinin of influenza virus) is the only mechanism for specific prevention of infectivity. Sometimes, antibody recognizing a fusion sequence of an enveloped virus may contribute. Frequently, neutralizing antibodies recognize discontinuous epitopes which present a tertiary or quaternary conformation. Sometimes, an epitope is a linear amino acid sequence, perhaps in the form of a loop (domain) with an —S—S— linkage.

*2 Limitation of Viral Replication*

As well as antibodies, several non-adaptive (non-specific) responses can limit the extent of viral replication during the first 24 to 48 h following agent administration. The list includes interferons, complement and a variety of cells including natural killer cells and cells with phagocytic activity.

*3 Clearance of (Recovery from) Infection*

In addition to the non-adaptive responses, those mediated by antibodies and effector T cells are important. Antibody-mediated mechanisms, such as ADCC or C′-dependent lysis, have been shown to reduce viral titers but in the absence of effector T cells, have not yet been shown completely to clear a viral infection (e.g. Askonas *et al.* 1982; Kris *et al.* 1985). In contrast, effector T cells and particularly $CD8^+$, class I MHC restricted cytotoxic T cells have been shown in numerous systems (Ada 1989) as primary (direct from the host), cultured or cloned preparations to reduce titers or to clear infectious virus. Cultured or cloned $CD4^+$ class II MHC restricted T cells may also have cytotoxic activity but this author is not aware of experiments showing that primary preparations have this activity.

*4 Generation of Memory Cells*

An essential component of any immune response is the generation of memory T and B cells. The pathway of generation of these cells is only now being adequately studied (e.g. Rajewsky 1989).

These events take place in a time-dependent manner (Ada 1990). For example, in the murine influenza model system, virus replicates in the lung, reaching high titers by days 4 to 6 and then declines so that no infectious virus is detected after 10 to 12 days. Cytotoxic T (Tc) cells appear by days 4 to 5, reach peak values at days 7 to 8 and no activity is detected in the lung after about day 14. Peak levels of memory Tc cells are found from about 14 days and persist for the life of the mouse. In contrast, IgM antibody secreting cells (ASCs) first appear at about day 6, and IgG and IgA ASCs at about day 10. Peak levels of ASCs and memory B cells occur between weeks 10 and 15 and both then decrease slowly but active cells are present for at least 80 weeks after the infection. As ASCs have a relatively short half life, this data is consistent with the interpretation that B memory cells are continually being recruited to form ASCs by antigen present and persisting on dendritic follicular cells in lymphoid follicles (MacLennan *et al.* 1989).

## Vaccines Function by Stimulating Adaptive Immune Response

A vaccine is usually administered before exposure to the wild-type agent occurs. The time interval may be weeks, months or years. To be successful, the vaccine should stimulate B cells (antibody formation), T helper (Th) cells and Tc cells. In the case of an antigenically stable infectious agent, neutralizing antibody is the immune parameter of most importance. Tc cell formation from vaccine-generated memory cells acts as a 'safety net'. However, if the major neutralizing epitopes show substantial antigenic variation, the organism will bypass the pre-existing antibody and replicate; in this case, a rapid Tc cell response by activated memory cells may be crucial in quickly destroying infected cells before new viral progeny is formed and released. In these situations, the fact that most if not all antigens of a virus may provide peptides which bind to MHC molecules and are recognized by the T cell receptor is important. As many of these derive from non-variable regions of the antigens, this is the major mechanism for ensuring cross protection to different viral subtypes.

## Four Requirements of the Ideal Vaccine

Following the above arguments, these requirements can be formulated as follows (Ada 1990): 1. activation of antigen-presenting cells to initiate antigen processing and production of interleukins; 2. activation of both T and B cells to give a high yield of memory cells; 3. to overcome the immune response in a population due to MHC polymorphism, generation of antibody to both two or three B cell epitopes (unless one is clearly shown to be immunodominant), and of Th and Tc cells to several epitopes is necessary; and 4. persistence of antigen, probably mainly on follicular dendritic cells in lymphoid tissue, where B memory cells are recruited to form ASCs, thus resulting in the continuing presence of antibody.

## New Approaches to Vaccine Development

Many live viral vaccines fulfil these criteria to a high degree. For the many vaccines needed to control diseases which are caused not only by agents such as HIV or papillomavirus but also by bacteria and parasites, new approaches to vaccine development are needed. The three main approaches are peptide synthesis, subunit antigen production by transfected cells and recombinant live vectors. A fourth approach, anti-idiotype preparations, has to date been disappointing.

To be effective, the new vaccines will need to fulfil the above criteria. Peptides *per se* are poorly immunogenic and usually need to be conjugated to a protein carrier which provides T cell help (e.g. Jones *et al.* 1988). Such preparations and subunit antigens usually need to be administered with an adjuvant, the role of which is at least two-fold. One role is to facilitate activation of the antigen-presenting cell. A second role is to act as an antigen depot.

## The Concept of Combination Vaccines

It seems most likely that vaccines of the future, made by any of the above approaches, will contain one or a small number of antigenic components. The hepatitis B virus vaccine, HBsAg, serves as a model. One approach may be more effective or acceptable at stimulating certain responses than another, e.g. use of a live vector is currently more effective at stimulating Tc responses than inactive proteins. Use of a particular adjuvant may be more effective than a live vector at inducing certain antibody responses. A combination of each, or one serving as a primer for the other, may achieve the ideal results.

A second consideration is an apparent anomalous situation with current vaccines. On the one hand, the antigen possessing antibody-neutralizing epitopes needs to retain its conformation so that B cells with the highest affinity Ig receptors are chosen. This occurs at two levels: recognition of antigen by (1) 'naive' B cells, and (2) memory B cells. In the latter case, antigen needs to persist for long periods in the correct conformation on the follicular dendritic cell membrane. There would seem to be a requirement for resistance to degradation in this situation.

On the other hand, ready degradation to peptides which associate with MHC molecules to form complexes recognized by T cell receptors would seem to be an advantage. As the internal antigens of enveloped viruses such as influenza, e.g. the nucleoprotein, are the richest source of such peptides (Ada & Jones 1986), it would make sense and not be a liability to the virus if these proteins were more susceptible than the surface antigens to proteolysis.

## Secondary Requirements for the Ideal Vaccine

Earlier in this paper a list of some additional five desirable characteristics of an ideal vaccine was given. It is as yet too early to assess properly the potential of the different approaches to vaccine development to fulfill most effectively these

attributes, but recombinant live vectors would seem to show particular promise in this regard. As an example, smallpox was eliminated using a vaccine which was extremely cheap (a few cents per dose), heat stable, readily administered and gave long-lasting immunity. Vaccinia virus can readily be manipulated to contain genes coding for several different antigens. Recombinant Salmonella preparations may offer similar prospects. Once such constructs are made and shown to be genetically stable, the cost of bulk production should be relatively inexpensive. During the smallpox eradication campaign, much of the vaccine used in the later stages was made in developing countries. It remains to be seen whether peptide-based or subunit preparations made using recombinant DNA technology will be competitive in these respects.

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