The pipe dream of new vaccines for old problems

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Vaccines are commonly invoked in discussions of public health policies since prevention is always felt to be better than cure, and since recent success stories of disease eradication or control such as smallpox are ascribed to vaccine use. New vaccine research is therefore a major component of many public health policies. However, it is important to recognise limitations inherent in vaccine research in order for its place in public health policy to be realistic.

Requirements for successful vaccines

For many infectious diseases, if someone recovers from one bout of the disease, they are not afflicted upon re-exposure. This immunity to the disease has two components. Firstly, the immune system responds to fight off the microbial infection. Secondly, it stores critical information about the microbe so as to mount an effective response more rapidly next time and eliminate the infection before illness sets in. A vaccine is a means of making the immune system believe that infection with a disease-causing microbial agent has occurred without actually causing disease, so that it acquires and stores the crucial information about the microbe needed to mount a rapid effective response when infection does occur.

In order to work, a vaccine must therefore generate sufficient magnitude (or quantity) and longevity (or memory) as well as the right type of an immune response. The degree of vaccine-mediated stimulation of cells of the immune system controls the extent of their expansion, and thus controls the magnitude of the immune response generated. However, since these cells are not only activated but also die upon stimulation (1), generating long-lived cells providing immune memory requires a delicate balance between activation and death. The type of immune response most effective also varies from infection to infection. Extracellular infections like pneumococci or streptococci are best dealt with by antibody responses. Intracellular bacterial infections such as the typhoid or the tuberculosis bacilli need activation of phagocytic cells. Viral infections necessitate killer immune cell stimulation.

Clearly, the ability to control each of these parameters while triggering an immune response through an externally administered vaccine is crucial for rational vaccine design. Unfortunately, while many elements of the controlling mechanisms involved in these processes are known (2), the level of sophistication of understanding is not high enough the permit any real prediction.

Uncertainties and limitations

Some examples might clarify this. The vaccine against smallpox is actually the cowpox virus which is related to smallpox and induces an immune response that protects against smallpox, but does not cause a severe disease unlike smallpox. Using the same principles, if a close relative of another disease-causing microbial agent is used, such as the BCG bacillus for tuberculosis, the success of the vaccine is far less than that of the vaccine for smallpox. However, none of the many possible explanations of why BCG fails to protect against tuberculosis in many situations while the cowpox vaccine against smallpox does succeed are sufficiently clear, detailed and certain to point to a rational solution of the problem (3,4). All that can be and is being done is to try other independent empirical ways to make vaccines against tuberculosis (5).

Another example is that of gut diseases. The agents of many diarrhoeal diseases do not penetrate the lining of the gut. Immunity against them, therefore, relies on antibodies secreted into the gut. Only the IgA type of antibodies can be efficiently secreted. However, there is currently no way of vaccinating people to generate reliable and efficient secretory IgA responses (6). Oral administration does in some instances lead to IgA responses. However, the vast numbers of food substances do not all generate such responses either. In fact, many of them make the immune system non-responsive to themselves (7). There is little comprehension of what properties make a substance immunogenic when given orally (8). In this situation, efforts at making either vaccines against enteric diseases or so-called edible vaccines are reduced to making hopeful designs and testing them out (9), with no progressive and rational approach to steady design improvement.

Limitations in estimating vaccine development costs

This means that there is no real way of predicting the progress of development of a vaccine against a given disease, and of telling in advance how effective a given approach is likely to be. All that can be done is to ensure that the approach is technically competent, and to hope for the best. This, I submit, is not a situation in which reliable estimates of the cost of the development of any new vaccine can be made.The issue is further compounded by the fact that that many diseases that are thought of as one disease are in fact a group of similar-looking diseases caused by unrelated or only distantly related microbial agents. Each of these agents is likely to need a separate vaccine developed against it, multiplying the problem of the uncertainty of vaccine-based solutions.

Such a non-estimatable cost cannot, in the nature of things, be less (or more) than a known cost, however large the latter is. Thus, it stands to reason that, given the current level of scientific ignorance, there is no basis for claiming with any certainty that developing new vaccines is a cheaper solution for a public health problem for which there is already an effective solution known. Infectious diseases transmitted via faecally contaminated drinking water, which account for a large part of the infectious disease load on public health systems in developing countries including India, are an obvious example. Such diseases account for a

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very large part of the infectious disease load on the public health systems of most developing countries including India. Clean assured water supply is an obvious and tested solution for this, and its cost can be estimated reliably, unlike the costs of developing new vaccines for all the different diseases involved.

Non-permanency of vaccine-based solutions

The example of immunity in the gut is also useful for making another point about the limitations of vaccines. An argument can be made that while clean water, hygienic surroundings and good nutrition have to be provided continuously all life long, a vaccine can simply be given once and the problem of that disease can be permanently solved for that individual at least. This is not quite correct. The reasons are related to the basic conundrum of a vaccine.

When a successful vaccine mimics a natural infection in persuading the immune system that the microbial agent is actually present and infecting the body, it will generate both immediate effects (called effector responses) to fight off the apparent infection, as well as the long-lasting memory responses that are the goal of the vaccine. The immediate protective effects, however, are no use, since the vaccine is only a harmless mimic; - no actual infection has taken place.

However, any effector response such as, say, an antibody response, persists for some time once triggered. If a real infection takes place during this period, this pre-formed antibody response will offer protection. This is what allows the vaccine against rabies to be effective. However, this does not mean that the new infection has actively recalled any protective immune memory. This kind of pre-formed effector response will last for only a short time, until the cells responsible die off. There is increasing evidence that effector and memory responses are independently controlled, and perhaps inversely related (10). Thus, the presence of an effector response such as an antibody response soon after vaccination is no guarantee that effective immune memory has also been triggered. This is particularly true of immunity triggered in the gut where, even when effector responses are generated efficiently, induction of immune memory is very poor.

In effect, many such vaccines will have very short periods of efficacy, defined by the period of persistence of the immediate effector response. Such vaccines are not permanent solutions; - they will need to be given again and again if continuous protection is to be maintained. This is further complicated by the fact that, just as populations of microbial agents can change to give rise to antibiotic-resistant strains, they can also change to evade vaccine-generated immunity (11,12). Thus, just as a continuous development of new anti-microbial drugs is essential, continuous development of new-generation vaccines is also likely to be essential, reinforcing the argument that new vaccines are not permanent solutions to old public health problems.

Limited significance of new vaccines in public health policies

It may be argued that, despite all these reservations, smallpox has been practically eliminated by vaccination. However, there are problems in applying this model to other infectious diseases. Smallpox has a short incubation period, a low frequency of subclinical infections and no environmental reservoirs outside the human body. This means that finding infected cases and containing spread of infection is relatively easy. Also, the smallpox vaccine is extremely effective, for reasons that are still ill understood. Under such circumstances, less than total coverage of a community by vaccination, if accompanied by careful case identification and infection containment, can eradicate the infection for all practical purposes. But assuming that all diseases are equally tailor-made to be vaccine-sensitive is likely to be counterproductive in planning public health policy.

It follows, therefore, that the development of new vaccines is not a pressing issue for public health purposes, both because it is unpredictable whether a vaccine that does not as yet exist can be made, and because the use of vaccines is unlikely to replace the real determinants of public health, such as safe water, sanitation, food, public hygiene, good housing, education, and the actual availability of medicines (as well as vaccines) along with information and medical service support.

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