

Vaccination – Past. Present and Future

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1. Life before vaccination.

In his book, *Guns, Germs and Steel*, Jared Diamond describes the history of civilisation over the last 13,000 years (1). A major feature was the great effect of infectious diseases on the survival of individuals, groups and even nations. If exposed to a disease epidemic when setting off to fight a battle, an army might not even make contact with the enemy due to the death of many soldiers. As people migrating from the Middle East settled in Europe and kept groups of animals such as cattle, the animal infectious agents over time (c.10,000 years) adapted to humans, increasing the human death rate. In time when some travelled and discovered Mexico, North America and even Australia, the mortality rate in indigenous populations due to the introduction of infectious agents could be as high as 50% so that within 100 years, the indigenous populations had decreased by up to 90%. Even 100 years ago, families often included many children because it was expected one or more would die from an infectious disease. That pattern would soon begin to change.

2. The early History of Vaccines and Vaccination

Smallpox is a terrible virus disease, killing about 40% of a naïve population. But at least, survivors never had a second infection. It was found some centuries ago that if a person was infected via a small scratch in the skin, a process called variolation, the mortality decreased by up to 90%. The real breakthrough came in the second half of the 18th century when it was realised especially in the UK that milkmaids escaped smallpox disease because of an earlier mild infection acquired from cows. In 1796, Edward Jenner injected a young boy, James Phipps, with cowpox and later deliberately with smallpox (2). The boy was completely protected, and so began the current era of 'artificial' immunisation. At that time, there was no understanding of how vaccination worked

A few vaccines became available in the early 20th century but most were made and used after the 1950s and are still being designed this century (2).

3. A Brief Outline of the Human Immune System.

There are two components – The innate system which exists in most multicellular organisms, and the adaptive system which is only found in vertebrates. It was originally

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thought that in vertebrates, these were quite separate and unrelated systems but it soon became apparent that they complement one another.

The Innate System.

The most important property of this system is that it comes into operation as soon as an infection is initiated or foreign material gains entrance to the body. It contains a number of cell types including dendritic cells, natural killer (NK) cells and macrophages. These cells secrete soluble factors, some called cytokines which can react with and influence other cells. Anti-bacterial factors also occur in many mucus membranes and the skin. Phagocytic cells such as macrophages, can take up and destroy foreign material including proteins especially if they had become linked to some of a group of factors called complement. In some situations, infected cells may be recognised and killed by NK cells. Another cell type, dendritic cells (DC), are most important because they 'present' foreign antigens to an important cell of the adaptive system, T lymphocytes, which are then activated and make very important protective responses. The DCs possess some special receptors which can recognise 'foreign patterns', such as molecules in a bacterial extract. When some bind to one of these receptors, the DC is activated and becomes a very effective presenting cell, resulting in a powerful immune response.

The Adaptive Immune System.

Towards the end of the 18th century, it was found that when a person was infected by viruses or bacteria, new proteins were formed and found in the blood. On transfer to another person, they would prevent infection by the same virus or bacterium. They were called antibodies and were formed by lymphocytes, a cell type which is a major cellular component in lymph vessels feeding into lymph nodes. Antibody prevents infection by binding to the relevant antigen on the surface of the infecting agent and so prevents it from entering cells. Some antibody proteins could be very large, e.g., IgM, (M. Wt, 900,000). Most types such as IgG, (lymph nodes), IgA (formed and secreted at mucosal surfaces) and IgE are smaller, M. Wt., 150,000). For many years, it seemed as though these different antibodies could be made by B lymphocytes (B, coming from bone marrow) without any help from other cells. Then in the early 1960s, an Australian immunologist, Jacques Miller, found by chance that if he removed the tiny thymus gland from a day old mouse, the mouse would die from infectious diseases because it now made a very poor immune response. He showed that the tiny thymus was the source of another class of lymphocytes (3), T cells which 'helped' B lymphocytes make IgG, IgA, IgD and IgE antibodies. Meanwhile, it had become clear that B lymphocytes made a very wide range of antibodies with different specificities which would bind antigens. In 1957, Macfarlane Burnet published the completely novel but astonishing proposal that an individual B lymphocyte made antibody of a single specificity (The Clonal Selection Theory, 4). It took 10 years to show this was correct and Burnet was honoured at the 1st International Congress of Immunology..

A critical finding was that after becoming active 'effector' cells, B or T lymphocytes could in a few weeks convert to become memory cells which had a very long life and could be quickly re-activated by a second similar infection to become effector cells again.. The basis of all current vaccines to date is to make sufficient antibody of the appropriate specificity to prevent or greatly minimise an infection.

As well as making 'helper' T lymphocytes, the thymus makes another cell type, the cytotoxic T lymphocyte (CTL, or killer T cell) which, during an infection, can rapidly

recognise and kill infected cells in the body. Like antibody formation, some 'helper' T cells are necessary for the formation of active CTLs. When infected by an agent for the first time, the sequence of formation of these immune cells in the body is first helper T cells, then CTLs and finally antibody. Often, CTLs can control and then clear the infection before sufficient antibody can be made to do this..

4. Types of Vaccines and currently registered members in each class..

The first part provides pertinent information about the different types of vaccines.

(i) Live attenuated microorganisms. The virus or bacteria are treated in different ways so they lose their ability to cause disease (ie., attenuation), but retain the ability to infect cells, to produce progeny and to induce a strong immune response, including both antibody and CTLs. Most such vaccines are highly effective.

(ii) Inactivated whole virus/bacteria. The agent is treated so that it is no longer infectious. Often a larger dose must be given to induce sufficient antibody, and usually, CTL formation does not occur.

(iii) Subunit and conjugate vaccines. Antibodies that block infectivity of viruses or bacteria recognise only surface antigens, either proteins or largely carbohydrate. There is increasing interest in isolating such preparations for use as a vaccine against the whole infectious agent because they would probably cause very little side-effects.. While the immune system recognises proteins and peptides very well, carbohydrates are poorly recognised. Some

bacteria take advantage of this by coating their external membrane with carbohydrate and they are particularly dangerous for very young children. A complex made by isolating the carbohydrate and attaching it to a protein, called a conjugate vaccine, is much more efficient at inducing anti-carbohydrate antibody.

Other than those delivered by a vector, most viruses and bacteria infect via a mucosal membrane, eg., the respiratory tract, the gut. In contrast, many vaccines are delivered by injection. One advantage of this method is that the recommended dose can be more accurately administered. Combinations of some vaccines are used as this limits the number of injections. Great care is taken to make sure each component works well.

A list of currently available viral and bacterial vaccines is presented in Table 1. Two early carbohydrate vaccines are not listed because the corresponding more recent conjugate vaccines are far more efficient. For example, within one year after the introduction of a *Neisseria meningitidis* serogroup C conjugate vaccine in the United Kingdom in 1999, the incidence of meningitis in young children and teenagers was reduced by more than 90%.(5).

5. Are Vaccines Safe?

Safety and efficacy are the two crucial properties of any vaccine. Of course, a vaccine would not be used unless it was effective in preventing disease following a later exposure to the 'natural' infectious agent. But a high effectiveness would count for little unless it was also very safe. For example, the first rotavirus vaccine released in the USA was highly effective but was found to induce a significant side effect, intussusception (collapse of the intestine, requiring surgery), at a rate of about 1/10,000 immunisations. The vaccine was promptly withdrawn. Members of anti-vaccination lobbies make a habit of claiming that many vaccines are unsafe. For example, when a second dose of MMR containing the measles vaccine was introduced in the late 20th century, there was an increase in cases of autism in young children at about the same time. Anti-vaccination groups claimed the increase in autism was caused by the increased use of the measles vaccine. Up to 10 different specialist committees subsequently showed there was no

relationship between the two events. Similarly, there is no clinical or scientific evidence that any vaccine causes a specific allergy, asthma, multiple sclerosis or the sudden infant death syndrome (5).

During testing, a new product undergoes three clinical trials of increasing size which it must pass before it can be considered for registration or licensing. For those with concerns about vaccine safety, the Commonwealth Department of Health issues documents answering the many myths like the above made about immunisation.(6).

6. . Are Vaccines Effective?

Many countries keep records of the use of vaccines in their population. The USA has a particularly detailed record and the data for the incidence of some diseases, before and after immunisation are given in Table 2. The data for measles is very impressive. From 1913 when records were first kept, there was never less than 100,000 cases each year and an epidemic occurred about every three years as groups of susceptible babies and infants became available for infection. This stopped dramatically in the 1960s when the vaccine was introduced. After the introduction of a second dose of vaccine at the turn of the century, transmission in the USA of this highly infectious agent stopped. Clinical cases of the disease in the country subsequently are due to infected visitors.

The data in Table 2 show that immunisation is one of the most successful achievements of medical intervention (7). A personal experience is telling. In recent years, I have lectured on this topic to over 800 final year high school students. When asked whether a young brother or sister has died from an infectious disease, not one has said - yes. In contrast, when I was very young, tuberculosis and meningitis claimed two out of five of my cousins.

7. Some difficult infectious agents; emerging and re-emerging diseases.

There are about 80 Infectious agents, including about 10 parasites, which can cause disease in humans (7). Apart from those in Table 1, attempts to make vaccines are being made against most of the remainder, and many are likely to be successful. There are some which have resisted all attempts to date, even for as long as 40 years. The three which are the most important are the human immunodeficiency virus (HIV, which causes AIDS), the bacterium, *Mycobacterium tuberculosis* and the parasite, Plasmodium, which causes malaria. Each has learnt how to evade the different components of the immune response, in part by developing great antigenic variation.

HIV is one of about ten emerging diseases, infecting humans recently for the first time.(8). West Nile virus is now called a re-emerging virus. Confined to Africa for centuries, it has recently reached and spread across the USA.

8. The future

New Vaccines. Among a long list of vaccines being developed, some of the agents causing the diseases are potentially highly dangerous. Among the viruses are Bird flu (H5N1), Dengue, Epstein-Barr, Hepatitis C, HIV, and Respiratory Syncytial viruses; among the bacteria, *Haemophilus ducreyi* (an STD), *Helicobacter pylori* and *Neisseria gonorrhoea*; and among the parasites, Malaria, Filariasis, Schistosomiasis and *Treponema pallidum* (syphilis).

.New approaches to immunisation. (i). Chimeric live vectors. Some DNA in a viral or bacterial vaccine is deleted, and replaced by DNA coding for one or more antigens from a disease agent. A strong immune response is made to the inserted antigen(s). (ii). Immunising with DNA coding for an antigen seemed attractive. Though it worked well in mice and monkeys, it gave poor responses in humans. (iii) A new approach, the prime/boost concept is promising. DNA coding for an antigen is inserted in two different live vectors. The host is primed with one chimeric vector and the response then boosted with the other chimeric vector. The results to date are promising. (iv). An infectious virus inactivated by exposure to gamma irradiation, still gives a strong antibody *and* CTL response, potentially a very safe technique.

The prospects for controlling/curing cancer. Cancers grow because they have learnt how to evade the immune response.. A viral infection causes some – e.g., hepatitis B virus and liver cancer, papilloma virus and cervical cancer, and these cancers have been prevented by vaccinating against the virus (e.g.). It is a very different story with the other cancers. It is a very active field, using antibodies, CTLs or pre-activated dendritic cells to induce a strong immune response. A major difficulty is to find antigen(s) which are specific to the cancer cells so that vaccination would not harm other cells. Prostate cancer cells have carbohydrate side chains specific for those cells, so this is a promising lead. But overall, progress is slow.

Table 1. Currently Registered Viral and Bacterial Vaccines.

<u>Viral</u>	<u>Bacterial</u>
<u>Live attenuated.</u>	
Vaccinia (smallpox)	<i>BCG</i>
Polio(OPV)	<i>Salmonella typhi</i>
Yellow fever	<i>Vibrio cholerae</i>
Measles	
Mumps	
Rubella	
Rotavirus	
Varicella Zoster	
Influenza (cold adapted)	
<u>Inactivated whole organism</u>	
Influenza	<i>Bacillus anthracis</i>
Polio (IPV)	<i>Bordetella pertussis</i>
Rabies	<i>Coxiella burnetii</i>
Japanese encephalitis	
Hepatitis A	
<u>Subunit</u>	
Influenza	<i>Salmonella typhi Vi</i>
Hepatitis B (HepB)	<i>Bordetella pertussis</i>
<u>Conjugate</u>	
	<i>Haemophilus influenzae</i> , type b (Hib)
	<i>Streptococcus pneumoniae</i> (heptavalent)
	<i>Neisseria meningitidis</i>
<u>Toxoids</u>	
	<i>Corynebacterium diphtheria</i>
	<i>Clostridium tetanus</i>
<u>Combinations</u>	
Measles Mumps, Rubella (MMR)	<i>Diphtheria, tetanus, pertussis</i> DTPw (w = whole organism) DTPa (acellular), DTPa, Hib, HepB, IPV.

Table 2. Vaccine efficacy (percent decrease in the incidence of different infectious diseases) in the USA, as assessed by comparing maximum morbidity levels before vaccine availability and the levels some years after compulsory vaccination was introduced.

Agent	Before vaccination		After vaccination		
	No of cases*	Vaccine available (widely used)	Number of cases		Decrease in disease incidence
			1996	2003	
Diphtheria	206,919	1921 (1942)	1	1**	>99.9%
Measles	894,134	1941 (1861)	500	56	>99.6%
Mumps	152,200	1968 (1971)	600	231	>99.6%
Rubella	57,686	1969 (1971)	210	7	99.6%
Pertussis	265,269	1935 (1945)	6,400	11,647	>94%
Poliomyelitis	21,269	1952 (1952)	0	0	100%
Paralytic Haemophilus	20,000	1984 (1987)	1,065	259	>99%

*During a major epidemic, **Calculations based on 2002 figures. Dates in parenthesis indicate the year the vaccine was widely introduced. MMR vaccine was introduced in 1971. IPV (Salk) vaccine in 1952 and OPV (Sabin) in 1963.

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