LITERATURE REVIEW OF VACCINE AVAILABLE IN BANGLADESH

This report presented in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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APPROVAL

This Project**,Literature review of Vaccine available in Bangladesh** submitted by Noor Jahan Akter to the Department of Pharmacy, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that, this project report is done by us under the supervision of **Md. Arifur Rahman, Assistant Professor,and Headd** Department of Pharmacy, Daffodil International University, impartial fulfillment of the requirements for the degree of Bachelor of Pharmacy. I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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DEDICATION
TO
MY PARENTS & BROTHERS

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ABSTRACT

Vaccine-preventable infectious diseases may be introduced into the healthcare setting and pose a serious risk to vulnerable populations including immune compromised patients. Healthcare providers (HCPs) are exposed to these pathogens through their daily tasks and may serve as a reservoir for ongoing disease transmission in the healthcare setting. The primary method of protection from work-related infection risk is vaccination that protects not only an individual HCP from disease, but also subsequent patients in contact with that HCP. Individual HCPs and healthcare institutions must balance the ethical and professional responsibility to protect their patients from nosocomial transmission of preventable infections with HCP autonomy. This article reviews known cases of HCP-to-patient transmission of the most common vaccine-preventable infections encountered in the healthcare setting including hepatitis B virus, influenza virus, Bordetella pertussis, varicella-zoster virus, measles, mumps and rubella virus. The impact of HCP vaccination on patient care and current recommendations for HCP vaccination against vaccine-preventable infectious diseases are also reviewed. Vaccines are among the most cost-effective interventions against infectious diseases. Many candidate vaccines targeting neglected diseases in low- and middle-income countries are now progressing to large-scale clinical testing. However, controversy surrounds the appropriate design of vaccine trials and, in particular, the use of unvaccinated controls (with or without placebo) when an efficacious vaccine already exists. This paper specifies four situations in which placebo use may be acceptable, provided that the study question cannot be answered in an active-controlled trial design; the risks of delaying or foregoing an efficacious vaccine are mitigated; the risks of using a placebo control are justified by the social and public health value of the research; and the research is responsive to local health needs. The four situations are: (1) developing a locally affordable vaccine, (2) evaluating the local safety and efficacy of an existing vaccine, (3) testing a new vaccine when an existing vaccine is considered inappropriate for local use (e.g. based on epidemiologic or demographic factors), and (4) determining the local burden of disease.

Chapter 1: Introduction

1. Introduction of Vaccine

T-cell memory is very important for long-lasting immunity, because T-cells control both humoral and cell mediated immunity. When the immune system recognizes a foreign antigen for the first time, an immune response isproduced. When T cells are involved, immunological T-cell memory is produced. When the body encounters sameantigen subsequently, a stronger immune response is produced. This is because of existing immunological memory against that antigen. Further antigenic stimulus increases the immune response. First antigenic stimulus is “priming”whereas subsequent stimuli are “booster”. This is the principle of active immunization.The term “vaccine” was coined by Louis Pasteur to commemorate first successful immunization against small poxby Edward Jenner. The term vaccine was derived from “vacca”, meaning cow, since Edward Jenner used cowpoxvirus (Vaccinia) to prevent smallpox infection. Vaccination involves deliberate exposure to antigen under conditions where disease should not result. Vaccination is aimed at inducing active immunity in an individual, so that subsequent contact with the microorganism following natural infection induces strong protective immune response.The protective immunity may involve secretion of neutralizing antibodies or production of memory CTL or Th1 cells.The use of vaccines is now being extended to immunize against tumors or to block fertilization (contraceptivevaccines). A vaccine is a suspension of whole (live or inactivated) or fractionated bacteria or viruses that have been rendered nonpathogenic, and is given to induce an immune response and prevent disease. Even though no vaccineis entirely safe or completely effective, their use is strongly supported by their benefit-to-risk ratio.

2.Chapter two: History of Vaccine

2.1:Early History of Vaccine: Vaccinology is a complex multidisciplinary science that is partly rational and partly empirical. It engages basics and breakthroughs in achieving practical and licensable products. Understanding and comprehending the specifics of vaccinology may be facilitated by review of its total history.Fig. 1 provides a diagramatic outline of the history of vaccines. Progress in the evolution of whole or sub-progress from the start of the scientific era followed by enlightenment derived from rational empiricism and transition to the modern era. The modern era has been the most productive of all, providing many new vaccines and technologies that have led to the contemporary period and to what the future may bring. Progress, for any particular time period, is rate limited by the kind and amount of finance al support it receives, as shown on the left vertical columns of the diagram.In the beliefs of ancient peoples (Table 1), diseases were infected on mankind by intangible and capriciousdeities as punishment for ill defined trans gressions.Fear of destruction by disease became an effective tool used by rulers, politicians and their shamans to instillterrors, which would prove useful in controlling human behavior in the long climb from early tribal to unit, live, killed or recombinant viral or bacterial vaccines can be divided into eras. The diagram depicts the civilized existence. Much of what was known to early civilizations about contagion, insect transmission, and sanitation was lost to Europe with the fall of Western Greco,Roman civilization following 400 AD and the onset of the Dark Ages. It was not to be revived infull until the nineteenth century. However, some, who were the forerunners of modern science, did discover microbial life forms, the relationships of environment to disease, and the fact that there was no secondnesses. Such heretical concepts revealed that man himself, rather than devils and demons, were the source of pestilence, and that solutions to problems might exist outside an appeal to the super natural.The ancient Chinese practice of preventing severe natural smallpox by inoculating pus from smallpox patients was introduced into Europe in the early eighteenth century. This procedure was known to Edward Jenner as was the fact that milkmaids were protected against smallpox by prior infection with cowpox. Laypersons, such as farmer Benjamin Justy, inoculated his family with the cowpox pus to prevent smallpox, well before the time of Jenner. .It was with

such background of knowledge that the English practitioner, Edward Jenner, conducted the first scientific investigations of smallpox prevention by human experimentation in 1796.

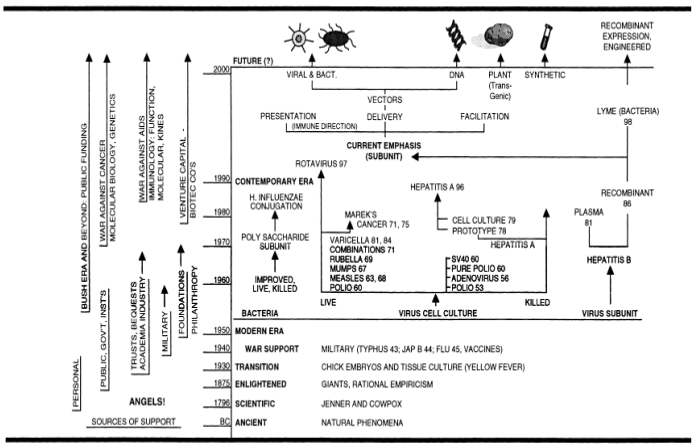


Fig. 1. Rise of vaccinology — BC to 2000.

These clinical studies proved that preinoculation of cowpox virus did prevent smallpox on challenge with virulent virus. From this beginning, the sciences of both vaccinology and immunology were born.During the nineteenth century, cowpox vaccination became a worldwide practice, especially in Europe and North America. But the principles learned from Jenner's seminal findings lay fallow for more than a century-and-a-half during which time no new vaccine had appeared. The field was sorely in need of proofs that would reject the theory of spontaneous generation and that would establish the germ theory of disease. Both of them were accomplished, in great measure, by The French chemist, Louis Pasteur.The fourth quarter of the nineteenth century (Table2) was a period of great awakening in which the meaningful science of vaccinology was born. It extended for more than four decades, into World War I. The giants of the early period were Pasteur, Koch, von Behring and Ehrlich. It was a period in which centralfocus was on bacteria, on medical application, and on empirical immunologic discoveries relating mainly toantibodies. Having noted attenuation of fowl plague bacteria by laboratory cultivation, Pasteur also observed that they induced resistance to subsequent challenge with virulent bacteria. Further studies gave rise to his development of credibly useful vaccines against anthrax, cholera and virus-caused rabies. It has been

suggested that Louis Pasteur's sudden and remarkable burst of insight into vaccines might have been aided substantially by his unacknowledged acquaintance with the pioneering concepts of Auzias-Turenne,which were published several years earlier.Robert Koch, in Berlin, was the master of pure culture and killed vaccines of useable quality had been evolved. In addition to those already mention.

Table 2
Vaccinology — 1875 through World War I and 1930

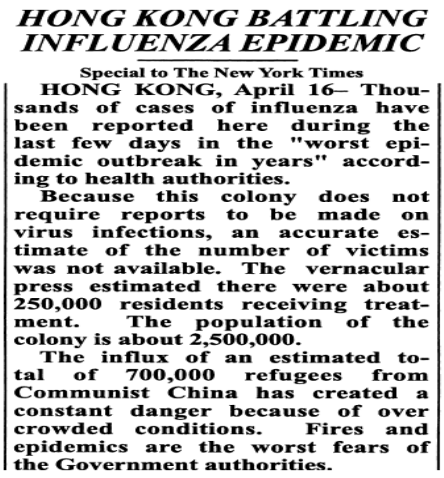
Great awakening 1875 — discovery and rational empiricism. Focus on bacteria and antibodies (rabies virus exception).
Giants were
Louis Pasteur — immunoprophylaxis, attenuation.
Robert Koch — methodology, etiology, hypersensitivity, postulates.
Emil von Behring — antibodies and immunotherapy.
Paul Ehrlich — specific receptor—ligand binding, specific chemotherapy, antibody quantificaton.
By 1929:
Humoral immunologic phenomena described
Immunotherapy dominates the field
Credible and useful vaccines
Smallpox and rabies
Killed and/or attenuated typhoid, shigella, cholera
Plague, diphtheria, tetanus, pertussis, and tuberculosis

Table 3
Vaccinology — transition 1930–1948, including early studies on influenza and adenovirus agents and vaccines at Walter Reed 1948–1957

1931	*Goodpasture* — virus propagation on membranes of embryonated hens' eggs.
1935	*Theiler* — safe and effective yellow fever vaccine attenuated by passage in minced chick embryo cultures.
Squibb Virus Laboratories	
Early 1940s	*Cox's* formalin-inactivated embryonated hen's egg (yolk sac) typhus vaccine for European invasion.
1944	Formalin inactivated mouse brain Japanese B encephalitis vaccine for Far East invasion, based on earlier Japanese and Russian studies and a Sabin report.
1945	*Wendell Stanley's* sharpless-purified chick embryo allantoic fluid-derived influenza virus vaccine. A paradigm for purified virus vaccines. Process and manufacturing developments at E.R. Squibb & Sons Labs. Military and civilian.
Walter Reed Army Institute of Research (WRAIR)	
1948–58	Discovery of progressive antigenic change (drift) and major change (shift) in influenza viruses by prospective and retrospective viral and seroepidemiologic studies. Detection of 1957 Pandemic; Vaccine development, 1957.
1953–57	Discovery of Adenoviruses (Epidemic — WRAIR; Latent — NIH) — 1953. Killed virus vaccine developed and proved effective(98%) — 1956. Commercial — 1958.

they included vaccines against typhoid fever, Shigellosis, tuberculosis, plague, diphtheria and tetanus. Pertussis vaccine was not to be developed until 1926. All these vaccines continue to be researched and improved to the present time. During this early period, resources for research (Fig.1) were severely restricted unless serving an important military need or an ability to obtain public or private subscription, based on public attention and acclaim. It is important to emphasize again that, for all time, the volume and speed of research accomplishment has been consistent with the amount of available support. they included vaccines against typhoid fever, Shigellosis, tuberculosis, plague, diphtheria and tetanus. Pertussis vaccine was not to be developed until 1926. All these vaccines continue to be researched and improved to the present time. During this early period, resources for research (Fig.1) were severely restricted unless serving an important military need or an ability to obtain public or private subscription, based on public attention and acclaim. It is important to emphasize again that, for all time, the volume and speed of research accomplishment has been consistent with the amount of available support.

2. Vaccines in transition from 1930±1950 (including1950±1957)The two decades between 1930 and 1950 (Table 3),which covered World War II, were a time of transition for what was to become a new era of vaccines. The large breakthrough of the period was Good pasture's demonstration in 1931 of viral growth in embryonated hens' eggs. From this came Theiler's safe and effective minced chick tissue vaccine 17Dagainst yellow fever that found enormous application



HONG KONG BATTLING INFLUENZA EPIDEMIC

Special to The New York Times

HONG KONG, April 16— Thousands of cases of influenza have been reported here during the last few days in the "worst epidemic outbreak in years" according to health authorities.

Because this colony does not require reports to be made on virus infections, an accurate estimate of the number of victims was not available. The vernacular press estimated there were about 250,000 residents receiving treatment. The population of the colony is about 2,500,000.

The influx of an estimated total of 700,000 refugees from Communist China has created a constant danger because of over crowded conditions. Fires and epidemics are the worst fears of the Government authorities.

2.1.1**. Early research** at the E.R. Squibb & Sons Research Laboratories. At the Squibb Virus Laboratories growth of typhus Rickettsiae in the yolk sacs of embryonated hens' eggs, according to the Cox method, rapidly led to mass production of licensed typhus vaccines that were seminal to the health of military personnel during World War II. We at the Squibb Laboratories developed Wendell Stanley's influenza vaccine, which was purified by continuous flow centrifugation, and which became a paradigm for purified viral vaccines. In addition, using are port by Sabin, my colleagues and I were able to evolve and, rapidly, to develop a crude formalin-killed mouse brain-derived Japanese B encephalitis vaccine for commercial manufacture that was used in 1944 and1945 to protect the troops in the Pacific offensive of World War II.

2.1.2**.. Research** at the Walter Reed Army Institute of Research Having joined the Walter Reed Army Research Laboratories in Washington, DC in 1948, my first assignment was to devise means for detecting and preventing the then ``next pandemic'' of influenza. In the course of prospective and retrospective virologic and sero epidemiologic studies, I discovered [8±10] that there were both progressive and abrupt changes, with time, in the antigenic specificity of influenza virus that is now called drift and shift. Then, on April 17, 1957, an article (Fig. 2) appeared in The New York Times, which provided a first alert to influenza in Hong Kong. Virus studies allowed my colleagues and me to predict the occurrence of the Asian Influenza Pandemic of 1957 that would start in the Fall in the US with the resumption of school. It did occur on schedule. Collaborating with commercial manufacturers, it was possible to achieve production of 40 million doses of vaccine by Thanks giving when the Pandemic peaked and rapidly declined thereafter. An inadvertent shift in the etiology of a respiratory disease epidemic, which occurred during a field study of influenza in 1951, at Fort Leonard Wood, MO,left me with a huge collection of blood and throat samples from cases of non-influenzal acute respiratory illness.

Table 4
Modern era — bacterial capsular polysaccharide vaccines — 1950 continuing

Dominant vaccine research is polysaccharide subunit	
Pneumococcus	
By 1945	Antibody response is marker for type-specific immunogenicity and protective efficacy.
1946	Hexavalent vaccine licensed but displaced by antibacterials.
1964–1968	Effective chemotherapy may not prevent death (R. Austrian). Renewed vaccine research.
1977	14-valent vaccine licensed.
1984	23-valent vaccine licensed.
Meningococcus	
1963	Sulfonamide resistance creates military problem.
1969–1972	Walter Reed vaccine feasibility and protection shown.
1974–1982	Vaccine development and licensure: A 1974; C & A–C 1975; A–C–W135–Y 1982. Sporadic occurrence limits commercial interest.
Haemophilus influenzae	
1985	Polysaccharide vaccine licensed for older children.
Reality	Polysaccharide vaccines are poorly immunizing in young children.
Mid-1970s	Discovery, conjugation and protein elicits protective response in new born animals.
1987–1990	Licensure of diverse *H. influenzae* conjugate vaccines.
1992	Intensive work on all polysaccharide vaccines.
1998	New Subunit Lyme Disease Vaccine licensed to SmithKline Beecham.

This large team study, with its tactical support, was very expensive and it was necessary for me to accomplish something of value before the deed was discovered. A newly deceased military recruit netted me a warm trachea from which my colleague, J.Werner, and I prepared explane cultures of trac heallining that grew out ciliated epithelial cells. Inoculation of throat specimens from the Leonard Wood patients gave three isolates(types 3, 4 and 7) of a new virus that was propagable in series. This was the discovery of the adeno viruses. Discovery of the adenoviruses causing epidemic disease was made in my laboratory, while those causing persistent latent infection in tonsils and adenoids of children were made in Robert Huebner's laboratory, both in 1952. Enders' breakthrough propagation of poliovirus (showing below) in cells of embryonic tissues in 1949 opened the way to cultivation of viruses in cells in culture. A killed monkey kidney cell-grown epidemic adenovirus vaccine was developed in my laboratory and was proved to be 98% effective in a large controlled clinical study at Fort Dix, NJ, in1956. This was just four years after discovery of the virus. Killed adenovirus vaccine was licensed for commercial distribution in 1958 for pediatric application. Much of the support for research between 1930 and1950 derived from military initiatives and from the rise of Foundations, which gave philanthropic donations and supported laboratories such as those of the Rockefeller Institute. Between 1950 and 1985 (Fig. 1), many new vaccines were pioneered, developed, and put into clinical trials, a few with licensure delayed until the late 1980s and1990s. But after 1985, there was rapid decrease in the pioneering and achievement of licensable new vaccines. Modern era vaccines (Fig. 1) are divided into whole and subunit bacterial, viral recombinant subunit, and live and killed whole virus preparations using virus grown in cell culture. Most of the vaccines of this entire era were pioneered and first licensed

in our laboratories, where resources and a uniquely appropriate organization with central authority favored successes

2.1.3. **Bacterial vaccines**

Principal bacterial vaccines (Table 4) of the modern era focus on subunit capsular polysaccharide preparations, though much progress with attenuated whole bacterial vaccines has also been made. Pneumococcal vaccines, containing but a few sero types, were first licensed in 1946 but were discontinued shortly thereafter because of the introduction of therapeutic sulfonamides and antibiotics. Though highly effective in eliminating bacterial infections, these drugs did not prevent death in some effectively treated patients. The field of pneumococcal vaccine research was kept alive by the persistent efforts of Dr. Robert Austrian. We entered into pneumococcal vaccine research in the early 1970's and this resulted in development of 14- and 23-valent vaccines that were licensed in 1977 and 1984.Development of meningococcus vaccines was initiated by us at the request of the military, following the pioneering studies at Walter Reed [24] of prototype vaccines to circumvent the problem of sulfonamide resistance and resurgence of meningitis among recruits at army installations. Monovalent, bivalent and quadrivalent groups A, C, W135 and Y vaccines were developed and evaluated by us and were licensed between 1974

Table 5
Modern era — viral vaccines — poliomyelitis 1950

National Foundation — supports establishment of basics. Antibody is marker for protection.
Killed vaccine. Macacus renal cell culture grown and formaldehyde inactivation with first order kinetics.
1955 Licensure
Problems
Incomplete poliovirus inactivation — caused paralysis. Process change and released.
Variable and less than acceptable potency.
Indigenous wild viruses in kidneys — assurance of inactivation.
1960: Hitherto undetectable monkey polyomavirus discovered, SV_{40}. Resists total inactivation.
1962: SV_{40} virus eliminated.
1960: Merck's Purivax licensed. Purified standardized potency vaccine. Discontinued for commercial reasons.
Live Vaccine. (nonneurotropic-attenuated).
1960 Licensure.
Problems
Retained or reversible neurovirulence.
SV_{40} contamination — removed.
Live vaccine became paradigm for poliomyelitis prevention and worldwide eradication.

and 1982.Polysaccharide vaccines, especially that of Haemophilus influenzae b, do not immunize young children. Discovery and presentation of an early paper inthe late 1960's or early 1970's by an unrecalled hero, that conjugation of polysaccharide with protein elicitsT cell help and immunizes infant animals, opened the door to development of the highly effective conjugate vaccines for young children by our own ,and many biologics companies, which continue to the present. Several highly effective conjugated H. influenzae vaccines have been licensed and are currently available. This same technology for conjugation is being applied at present to improve the immunizing capabilities of meningococcal and pneumococcal vaccines. Recombinant subunit polypeptide Lyme disease vaccine is new and licensure was granted to SmithKlineBeecham laboratories in 1998.

2.1.4. Viral vaccines

Vaccines against poliomyelitis (Table 5) were createdby programs that were funded and conducted under the auspices of the National Foundation for Infantile Paralysis. This foundation was an outgrowth and successor to the annual President Franklin Delano Roosevelt Birthday Ball for support of the Warm Springs Poliomyelitis Foundation A Rehabilitation Center.

2.1.5. Inactivated poliovaccines

The enabling breakthrough for the vaccine came with Enders' poliovirus propagation [18] in cell cultures of non neural tissue. Trivalent killed Salk polio vaccine was prepared using virus grown in Macacus monkey renal cell cultures and was licensed in 1955.This vaccine was faced with three immediate problems that related to incompleteness of poliovirus inactivation, to highly variable immunizing potency, and to the discovery by us of a new indigenous contaminating Macacus monkey polyoma virus, SV40. SV40,prior to that time, was undetectable. We also found that the SV40 virus was resistant (one in about 10,000particles) to total inactivation by formaldehyde in the poliovirus vaccine. Discovery of SV40 virus derived from our efforts to use kidneys for cell culture from Macacus monkeys that were not infected with the then ubiquitous presence of indigenous viruses. We identified and introduced the African Cercopithecus monkey to circumvent this problem. Renal cells

from this species were found to be highly permissive to viral replication with cytopathogenic change, and allowed us to detect the presence of hitherto undetectable agents. In particular, use of these cells permitted our detection ofSV40, virus that we later found to be oncogenic for baby hamsters. There was major disruption in killed polio vaccine manufacture when a small amount of live SV40 virus was found in the finished product. The problem was rapidly solved, however, by substitution of Cercopithecus monkey kidney cells that were free of indigenous viruses. Efforts to overcome the highly variable potency of the killed vaccine led us to develop a purified poliomyelitis vaccine with precisely standardized potency (Purivax). This product was licensed in 1960 but was ultimately discontinued for commercial reasons. Live oral fed Sabin polio vaccine was based on use of nonneurotropic poliovirus strains and was licensed in 1960. It also suffered the problem of SV40virus contamination, but, as for killed vaccine, the problem was easily solved by use of Cercopithecus monkey kidney cultures. The live vaccine retains, to this day, very low level neuro virulencefor man but rarely causes poliomyelitis in vaccines or in contacts of vaccines. In spite of this, live polio vaccine is the paradigm for poliomyelitis prevention and for worldwide poliovirus eradication.

2.1.5**. Live vaccines** for preventing pediatric diseases.The live attenuated pediatric vaccines, measles, mumps, rubella, varicella and their combinations were conceived by us as future possibilities in 1957, even though they were only theoretical dreams at the time. The importance

Table 6
Modern era — pediatric live virus vaccine — hurdles

Target: live attenuated vaccines: measles, mumps, rubella, varicella, combinations.
Common hurdles
Discover — grow virus in acceptable cell culture.
No animal models, no markers of attenuation.
All tests in children — decisions by judgment.
Preparation of numerous passage level vaccines of commercial quality.
Testing by judgment starting with likely most attenuated and working backward to acceptable balance in reactivity and immunogenicity.
Retention of acceptance of research by scientific and regulatory committees (overcoming objections, e.g., varicella).
Elimination — avoidance of viral contaminants.
Huge and long-term vaccine preparation and testing.
Protective efficacy in controlled studies.
Safety validation 10–20,000 susceptibles.
Safety for susceptible contacts.
Retained protection — long term.
Vaccine stable on storage and distribution.
Combined vaccines — no increase in reactogenicity, and formulation adjustment to prevent interference.

Table 7
Modern era — pediatric live virus vaccines — notable problems and solutions

Measles — chick embryo cell culture.
Reduce reactions.
Coadministration of immune globulin.
Further attenuation (no globulin).
Eliminate avian leukemia virus from cultures — development of experimental leukemia-free flocks.
High-level potency and safety.
Mumps — chick embryo cell culture.
Jeryl Lynn strain lacks neurovirulence.
High-level potency — nonreactogenicity.
Rubella — discovery — propagation in duck cells.
Rapid and reliable attenuation.
Nontransmission to susceptible adult contacts.
Bivalent and trivalent formulations
Acceptable potency and reactogenicity.
Very successful clinical acceptance.
Flagship pediatric immunogens.
Varicella — all aspects — worked out with KMcC strain by 1981.
Virus refused to achieve acceptable balance of reactogenicity vs. immunogenicity on application of attenuation procedures.
OKA strain substituted.

of the concept was, eventually, to provide a simple solution to a large segment of the pediatric viral disease problems.The research and development (Table 6) of the individual pediatric live virus vaccines were faced with numerous hurdles, usually common to all of them. One hurdle was to develop large numbers of different passage level vaccines, of commercial quality. These were tested clinically to find a level with acceptable toxicity and adequate potency, starting at highest passage level, lowest virulence, and working backwards. With no animal models and no markers of attenuation, all tests needed to be done in child volunteers. Detailed clinical observations and the exercise of judgment were the principal guidelines. Efficacy of each candidate vaccine was proved in two placebo controlled protective efficacy trials. Safety validation of each vaccine was usually made in tests in 10 to 20,000 susceptible children and their susceptible contacts. Suitable vaccines needed to provide long-term protection. The combined vaccines required dose adjustments to retain the same favorable immune response as for the individual vaccines when given alone. Finally, all vaccines needed to be stable on storage and on distribution. Each of the live virus vaccines had individual problems and solutions (Table 7) that are discussed below.

2.1.6. Measles vaccine

Seminal to preparation of the measles vaccine was the need to eliminate the ubiquitous avian leukemia virus contamination of the hens' eggs used to provide the tissue needed for cell culture. This problem was solved through the development of leukemia free chicken focks. Further, the original Enders' Edmonston B measles virus had excessive virulence for children that we were able initially to reduce by co administration of measles immune globulin. The problem was better solved by our development of the further attenuated Moraten line of measles virus that required no immune globulin. High-level potency and safety needed to be proved for the modified Moratenvirus substrain as had been required for the original virus.

2.1.7. Mumps vaccine

The Jeryl Lynn mumps virus isolate that was recovered and attenuated in our laboratories provided avery suitable nonneurovirulent and highly immunogenic vaccine.

2.1.8. Rubella vaccine

Rubella vaccine development was aided by our breakthrough discovery of propagation and of rapid and reliable attenuation of the virus in duck embryo cells in culture. An important attribute was lack of communicability of the vaccine virus to susceptibles who were in contact with vaccinated persons.

2.1.9. Combined MMR vaccine

Combined bivalent and trivalent formulations of measles, mumps and rubella vaccines were developed that were safe and effective in all respects. The trivalent vaccine, MMR, became the flagship for pediatric immunization and continues to the present with very significant cost savings.

Table 8
Modern era — Marek's chicken cancer vaccine

Marek's disease, a neural lymphoma or visceral lymphoma of chickens (range paralysis) is caused by a herpesvirus. Economic loss to poultry industry is large, through lowered productivity (eggs and meat) and condemnations at slaughter.	
1970	Burmester discovers turkey herpesvirus antigenically related to chicken Marek's. Burmester virus causes no disease in chickens but protects against Marek's. After long and complicated research to establish safety and efficacy for chickens and safety for man in food consumption, two highly effective vaccines were developed in our laboratories.
1971	Frozen infected cell vaccine.
1975	Purified free virus vaccine, dried. This was the world's first licensed vaccine against any cancer. It revolutionized the economics of the poultry industry!

2.1.10. Varicella vaccine

Our KMcC varicella vaccine, that was studied for more than 15 years, was used to pioneer and to develop all aspects of chickenpox vaccine preparation and protection, but for one aspect. It proved impossible to achieve acceptable potency for KMcC at an attenuation level, which also had acceptable react ogenicity. The Japanese Oka strain was successfully substituted and brought to licensure. It is being readied for addition to the trivalent MMR vaccine.

2.1.11. Live vaccines against Marek's chicken cancer Marek's disease (Table 8) is a neural and viscerallymphoma of chickens that causes huge economic losses to the poultry industry through lowered productivity and condemnations at slaughter. Burmester and colleagues' turkey herpes virus]was shown to protect against the antigenically related Marek's herpesvirus, without causing disease in chickens. We developed and licensed infected frozencell Marek's vaccine in 1971, and purified dried virus vaccine in 1975. These licenses were granted by the United States Department of Agriculture after long and complicated studies to prove protective efficacy and safety for chickens, and acceptability for human food consumption as well. This was the world's first licensed vaccine against any cancer and it revolutionized the economics of the poultry industry.

2.1.12. Discoveries and development of vaccines against hepatitis Large-scale laboratory and field studies were initiated by our laboratories in the early 1960s with intent to discover viruses causing hepatitis A and B.

2.1.13. Hepatitis A virus and vaccine (Table 9) In 1973, we published our earlier isolation of theCR326 strain of hepatitis A virus in marmosets. The GB virus that had been isolated previously by Freidrich Deinhardt in marmosets has been founder recently to be a Flavivirus and not the virus of hepatitis A. Deinhardt's GB virus discovery is of special significance since it predates that of the discovery of hepatitis C Flavivirus. Studies to characterize ,completely, hepatitis A virus and hepatitis A disease were carried out in our laboratories making it possible to write a new chapter on infectious hepatitis. A highly protective formaldehyde-killed virus vaccine was developed and reported by us in 1978 in which we used virus that was purified from infected marmoset liver. In 1979, our laboratory made the breakthrough discovery of cell culture propagation of hepatitis A virus that opened the door to preparation of a vaccine for use in man. Such killed virus vaccine, based on the 1978 marmoset liver prototype procedure, proved highly safe and protective in controlled field studies. The vaccine was licensed in1994 and is now used routinely in many parts of the world. We also pursued long-term development of live virus vaccines.

O. Hepatitis B virus vaccines (Table 10)

2.1.15**. Plasma-derived hepatitis B vaccine**

The discovery in 1965 by Blumberg and by Prince of the surface antigen of hepatitis B virus present in the blood of human carriers of the infection, opened the door to a hepatitis B vaccine. Starting with a near zero data base, probes were carried out in our laboratory beginning in 1968 to explore purification, yield, inactivation, safety and efficacy of a possible candidate hepatitis B vaccine using surface antigen purified from human carrier plasma. The processes that were evolved were successful. Hepatitis B virus does not propagate in vitro and tests for inactivation of surrogate viral agents in each of the multiple inactivation steps were used to assure safety from live hepatitis B virus and likely all possible microbial life forms that might be present in human blood. High level protective efficacy of the vaccine was proved, first in chimpanzee challenge studies and then in controlled clinical trials in man in 1980. The vaccine was proved safe and highly protective, and was licensed for general use in 1981. This was thirteen years after our intensive vaccine investigations were first initiated.

Table 9
Modern era – Hepatitis A virus vaccine

Early 1960s	Program initiated to discover viruses of hepatitis.
1973	Recovery of CR326 hepatitis A virus in marmoset monkeys. (Deinhardt's GB virus, originally believed to cause hepatitis A, was recently shown to be the earliest example of flavivirus, hepatitis, nonA–nonB (predating hepatitis C).
1978	Highly effective formalin-killed infected liver cell derived hepatitis A prototype vaccine shown safe and effective in marmoset and chimpanzee studies.
1979	Breakthrough cultivation in cells in culture opens door to vaccine for man.
1991	Cell culture-grown formalin-killed vaccine prepared using marmoset liver vaccine procedures.
1992	Safety and efficacy.
1994	Licensed.

2.1.16. Recombinant-expressed vaccine Supplies of acceptable human carrier plasma were in adequate to meet market needs and a cooperative study was established in 1975 with Drs. Rutter and Hall of the Universities of California and Washington to develop a recombinant expression system for producing hepatitis B antigen. Recombinant expression was achieved in yeast and cultivation and expression were optimized in our laboratories. The purified recombinant antigen was substituted for the antigen in the plasma-derived vaccine and was

shown to yield a product, which performed the same as the plasma derived vaccine. The recombinant hepatitis B vaccine was licensed in 1986, just 11 years after the first recombination studies were initiated. The two hepatitis B vaccines represent the world's first viral subunit vaccine, the first licensed vaccine to prevent human cancer, and the first recombinant-expressed vaccine. This vaccine, with the urging of the World Health Organization, is now being programmed for routine use to immunize all babies in more than 100 countries.

Table 10
Modern era — Hepatitis B virus vaccines

Early 1960s	Search for hepatitis viruses.
Plasma-derived vaccine	
1965	Blumberg and Prince discover surface antigen of hepatitis B virus in blood of carriers.
1968	Probes initiated for purification, inactivation, safety and efficacy.
1980	Efficacy proved.
1981	Vaccine licensed (after 13 years of research).
Recombinant yeast vaccine	
1975	Initiated collaborative studies with Rutter and Hall to develop vector-expressed hepatitis B surface antigen.
1982	Expression system in recombinant yeast. Antigen extracted, purified and substituted for plasma-derived antigen.
1986	Recombinant vaccine licensed.
Hepatitis vaccines represent	
World's first subunit vaccine.	
World's first licensed vaccine against human cancer.	
World's first recombinant expressed vaccine.	

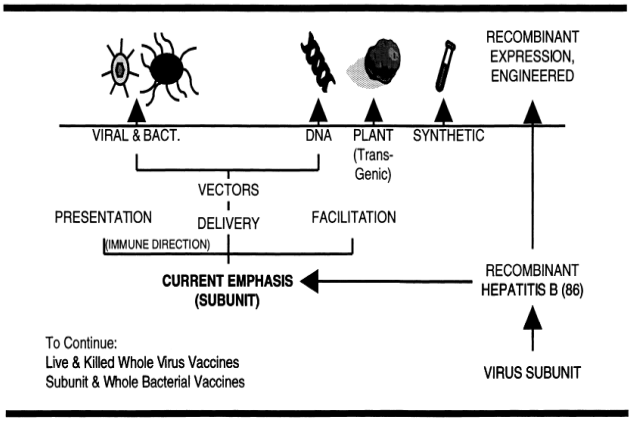


Fig. 3. Present and future vaccinology — building on past and recent discoveries.

2.1.17. **Contemporary era and future vaccines** Contemporary vaccinology (Fig. 3), at least for viral vaccines, is very complex and is dedicated largely to the subunit vaccine approach. Contemporary subunit vaccines are built on the same foundation and may be considered to be an extension of recombinant subunit hepatitis B technology, that was extensively pursued from the beginning in the attempt to develop a vaccine against AIDS. Save for the Lyme vaccine, no recombinant vaccine, other than that for hepatitis B, has been licensed to the present time. Whole live and killed virus and bacterial vaccines may also continue to be explored. Live Rotavirus vaccine, recently licensed to the Wyeth Lederle Laboratories, is such an example.The contemporary era is eagerly begging for new vaccines to control more than 20 diseases, especially tuberculosis, malaria, hepatitis C and AIDS. Pioneering new vaccine development, in the period since 1985, has been remarkably sterile and filled with`` gonna's and promises" but few successes. The real question of the present is what will drive the future? Belated recognition of the importance of cell-mediated as well as humoral effector mechanismsin the immune response has initiated a whole new era of vaccine research that promises rewards greatly in excess of anything we have seen in the past. Seminal to this new era are the remarkable advances made in defining and understanding immune function. The necessary achievement of both humoral and cell mediated immunities has been clearly established, as revealed in numerous publications. New vaccines rely on identification of appropriate antigens and epitopes. Importantly, they must rely on the ``what" to present to the immune system as well as the ``how" to present. To the current period, the cart has been mostly in front of the horse with exquisite advances in antigen presentation technology and earth of knowledge of what to present. The what to present will be a major problem for vaccines such as that against AIDS until more simple and more ancient methodologies for antigen and epitope discovery and identification have been achieved. The how to present, as illustrated in Fig. 3, is already filled with new and exciting possibilities. Central to it all will be molecular genetics with continued evolvement of eukaryotic cell expression following the breakthrough technology used for recombinant hepatitis B vaccine. Added to this is the immense promise that live recombinant microbial and DNA vectors may give. Endogenous expression and presentation by antigens in transfected dendritic cells give immense opportunity for development of vaccines to prevent infections as well as to treat persistent

infections and cancer. Transgenic plant tissues might provide a possible answer to the need for cheap and easily administered vaccines for the huge populations of the developing world. Improved synthetic chemistry, creating appropriate antigens and epitopesin linear tandem composition, or in multiple arrays on folds, may also find a significant role in the future. The platforms of knowledge developed during the 20th century are ripe for exploitation and for anticipated successes early in the 21st century. It is not unreasonable to be optimistic and to expect that what must be, will be!

2.2 History of Vaccines

No public health tool has been as successful and cost effective as vaccines at saving lives, particularly among the world's children. Over the last half of the 20th century, diseases that were once all too common became rare in the developed world, due primarily to wide spread immunization. Routine vaccination programs have prevented the deaths of hundreds of millions of people and saved billions of dollars in public health expenditures. Yet the role of vaccines in public health is often overlooked today. Then and now…

Smallpox: In the 20th century alone, smallpox was responsible for an estimated 300 to 500 million deaths ,more than double the number of people killed during the wars of that same period. As recently as 1967, the World Health Organization (WHO) estimates that 15 million people contracted the disease, and 2 million died that year. Small pox has since been eradicated, through the effective use of vaccines.

Polio: In the years following World War II, polio was the most feared disease among parents in the United States. In 1952, it is estimated to have permanently paralyzed 21,000 people in the United States alone. Since then ,immunization campaigns have reduced polio rates by more than 99 percent, down to 1,385 annual cases. The fight to fully eradicate polio worldwide continues.

Measles: Measles is far more contagious than smallpox, and in some children can be just as dangerous. Measles can cause deafness, blindness, encephalitis, and death. Between2000 and 2007, measles deaths dropped by 74 percent when several new vaccines were developed in a relatively short period. Their success in preventing diseases such as polio and measles was

nothing short of revolutionary, and large-scale vaccination campaigns soon followed. Although vaccination is now a routine medical intervention, supplying vaccines to the general public required a massive mobilization of resources and human endeavor, from the scientists who developed and tested vaccines, the manufacturers that produced them, the public health officials who advocated for them, to the governments that paid for them, and finally to the millions of people who rolled up their sleeves to participate. It was are mark able achievement, requiring tremendous effort from all concerned. These efforts paid off in a dramatic fashion. In 1967, the WHO spearheaded a massive immunization campaign against smallpox. Within ten years, this disease that had plagued human civilization for thousands of years had been vaccinated out of existence. Wild-virus polio, which once circulated widely in nearly every region of the world, is now present in only a handful of countries, without a case diagnosed in the United States since 1979.Measles, mumps, rubella, diphtheria, and pertussis were reduced from frightening epidemics to rare outbreaks within a few decades.

The paradox of success

As the prevalence of once-terrifying diseases decreased, so did the fear. Vaccines began to lose some of their luster. Only 50 years after vaccination became a standard rite of passage for children, it was taken for granted that a child born in the developed world would grow up without fear from the paralysis, brain damage, blindness, and death that plagued the generations before her. In addition, as years passed and infectious disease rates fell, concerns began to grow over vaccine risks and side effects, which led some to question the wisdom of mass vaccination. This scrutiny of vaccines had many positive effects; besides sparking a national movement to improve oversight of vaccine manufacture, it also led to better vaccine technology. Vaccines became safer than ever before. However, the criticism has had some negative consequences as well. Because people do not fear the diseases anymore, vaccine coverage is falling in some areas, worldwide. However, more than 18 million people continue to be infected by measles each year, resulting in 197,000deaths in 2007,primarily among children.

Rubella: Althoughrubella is a mildchildhood illness, It can cause severe birth defects in child reborn to mothers who contracted the disease in the early stages of pregnancy.The

introduction of a rubella vaccine in 1969 has greatly reduced the incidence of congenital rubella syndrome in the developed world, but the disease still causes approximately110,000 cases each year, and causes blindness, deafness, and mental retardation in thousands more.

Diphtheria: Diphtheria was once one of the most common causes of death in children. As recently as the 1920s,diphtheria infected an estimated 100,000 to 200,000 people per year in the United States and killed 13,000 to 15,000. While it is now rare in the US, diphtheria is re-emerging insome areas of the world and is responsible for about5,000 deaths each year in developing countries, primarily among children.

Pertussis*:* Pertussis, or whooping cough, causes spasmodic, uncontrollable coughing that persists for weeks. Before the arrival of the vaccine, pertussis infected an average of200,000 people a year in the United States alone. Although global rates have fallen significantly since the arrival of the vaccine, pertussis still kills almost 300,000 people every year.

The arrival of vaccines

Although the earliest smallpox vaccine was developed in 1796, vaccination of large groups of people remain edsporadic until the 20th century. The golden age of vaccine development did not come until after World War II, and diseases once thought beaten are making new in roads. The incidence of pertussis has increased nationwide inthe last 20 years, with more than 25,000 cases reported in 2005. In 2008, 131 cases of measles were reported in the U.S., the highest in any year since 1996. In addition, fear of litigation and market uncertainties have driven many drug companies out of the vaccine business, inhibiting innovation and occasionally creating shortfalls in vaccine supply.

Looking into the future

Despite several years of neglect, vaccines are once again gaining attention as vital solutions in the fight again stinfectious disease. Major efforts are under way to develop new vaccines against pneumonia, AIDS, tuberculosis, malaria, and diarrheal diseases like rotavirus. Introduction of these vaccines into the developing world has the potential to save millions of lives.

Properties of ideal vaccine:

• Provide long lasting immunity.

• Should induce both humoral and cellular immunity.

• Should not induce autoimmunity or hypersensitivity.

• Should be inexpensive to produce, easy to store and administer.

• Vaccines must also be perceived to be safe.

2.3 Vaccine Benefits

We and Our Community

Once our immune system is trained to resist a disease, we are said to be immune to it. Before vaccines, the only way to become immune to a disease was to actually get it and, with luck, survive it. This is called naturally acquired immunity. With naturally acquired immunity, we suffer the symptoms of the disease and also risk the complications, which can be quite serious or even deadly. In addition, during certain stages of the illness, we may be contagious and pass the disease to family members, friends, or others who come into contact with us. Vaccines, which provide artificially acquired immunity, are an easier and less risky way to become immune. Vaccines can prevent a disease from occurring in the first place, rather than attempt a cure after the fact. It is much cheaper to prevent a disease than to treat it. According to one U.S. analysis, for every dollar spent on the measles/mumps/rubella vaccine, 21 dollars are saved. Vaccines protect not only ourself but also others around us. If our vaccine-primed immune system stops an illness before it starts, we will be contagious for a much shorter period of time, or perhaps not at all. Similarly, when other people are vaccinated, they are less likely to give the disease to our. So vaccines protect not only individuals, but entire communities. That is why vaccines are vital to the public health goal of preventing diseases.

Chapter three: How Vaccine work?

The Immune System: To understand how vaccines teach our body to fight infection, let's first look at how the immune system fends off and learns from a naturally occurring infection. Then we'll examine how vaccines mimic this process. Imagine we are a dock worker on the piers of Philadelphia. The year is 1793. As you are unloading crates of tea and spices from an oceangoing ship, a mosquito bites you on the arm. This mosquito carries the virus that causes yellow fever, which the mosquito picked up when it bit a sailor who recently returned from Africa. So now you have thousands of yellow fever viruses swarming into our body. In fact, you have become part of an infamous epidemic that will claim the lives of 10 percent of the people in Philadelphia, and all that stands between we and a fatal case of yellow fever is your immune system. Our immune system is a complex network of cells and organs that evolved to fight off infectious microbes. Much of the immune system's work is carried out by an army of various specialized cells, each type designed to fight disease in a particular way. The invading viruses first run into the vanguard of this army, which includes big and tough patrolling white blood cells called macrophages (literally, "big eaters"). The macrophages grab onto and gobble up as many of the viruses as they can, engulfing them into their blob-like bodies.

Chapter Four:Vaccine Classification

Classification of vaccines

4.1.1.KILLED VACCINES

When it is unsafe to use live microorganisms to prepare vaccines, they are killed or inactivated. These are preparations of the normal (wild type) infectious, pathogenic microorganisms that have been rendered nonpathogenic ,usually by treatment with using heat, formaldehyde or gamma irradiation so that they cannot replicate at all. Such killed vaccines vary greatly in their efficacy.

Microorganism	Vaccine	Method	Route
Salmonella typhi	TAB	Heat, Phenol, Acetone	SC
Vibrio cholerae		Phenol	SC or ID
Yersinia pestis	Haffkine	Formalin	SC
Bordetella pertussis	-	Merthiolate	IM
Poliomyelitis	Salk	Formalin	IM
JE virus	Nakayama Strain	Formalin	IM
Rabies virus	Semple	Phenol	SC
	BPL	BPL	SC
	HDCV	BPL	IM or SC
	DEV	BPL	IM or SC
Influenza virus	-	Formalin	IM
Hepatitis A	HM175	Formalin	IM

Advantages:

• Safe to use and can be given to immune deficient and pregnant individuals.

• Cheaper than live attenuated vaccine

• Storage not as critical as live vaccine

Disadvantages:

• Since the microorganisms cannot multiply, a large number are required to stimulate immunity.

• Periodic boosters must be given to maintain immunity.

• Only humoral immunity can be induced.

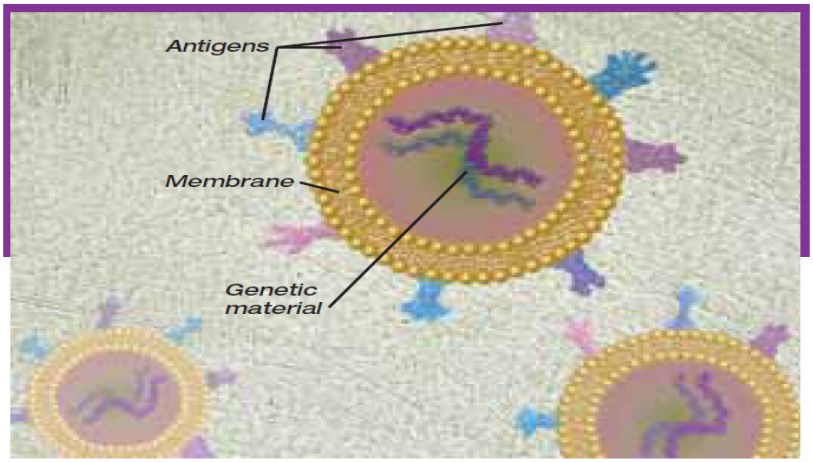
• Most killed vaccines have to be injected.

4.1.2LIVE ATTENUATED VACCINE

These vaccines are composed of live, attenuated microorganisms that cause a limited infection in their hosts sufficient to induce an immune response, but insufficient to cause disease. To make an attenuated vaccine, the pathogen is grown in foreign host such as animals, embryonated eggs or tissue culture, under conditions that make it less virulent. The strains are altered to a non-pathogenic form; for example, its tropism has been altered so that it no longer grows at a site that can cause disease. Some mutants will be selected that have a better ability to grow in the foreign host. These tend to be less virulent for the original host. These vaccines may be given by injection or by the oral route. A major advantage of live virus vaccines is that because they cause infection, the vaccine very closely reproduces the natural stimulus to the immune system.

Bacteria/virus	Vaccine	Method	Route
Vibrio	CVD103Hgr	Genetically modified	Oral
Salmonella	Ty21a	Genetically modified	Oral
Mycobacterium	BCG	Prolonged subculture	ID
Polio	Sabin	Passage in MK cells	Oral
JE	SA 14-14-2	Passage in weanling mice	IM
Yellow Fever	17D	Passage in chick embryo cells	SC
Influenza	-	Temperature sensitive mutant	IN
Mesales, Mumps, Rubella	MMR Rubella (Wistar RA 27/3)	Passage in fibroblasts cells	SC
Chicken pox	Oka/Merck	Human diploid cell cultures	SC
Small pox	Vaccinia virus	Naturally avirulent	ID

The influenza vaccine contains cold-adapted vaccine strains of the influenza virus that have been grown in tissue culture at progressively lower temperatures. After a dozen or more of these passages, the virus grows well only at around 25° C in vivo growth is restricted to the URT.



Live, attenuated vaccines use a weakened version of the microbe that has been changed to reduce or eliminate its potential to cause disease. This image shows the live microbe's antigens, membrane, and genetic material.

Advantages:

• Infectious microbes can stimulate generation of memory cellular as well as humoral immune responses.

• A single administration of vaccine often has a high efficacy in producing long-lived immunity. Multiple booster doses may not be required.

• Whole microbes stimulate response to antigens in their natural conformation. They raise immune response to all protective antigens.

• Some live vaccines can be given orally; such vaccines induce mucosal immunity and IgA synthesis, which gives more protection at the normal site of entry.

• Oral preparations are less expensive than giving injections.

• They can lead to elimination of wild type virus from the community

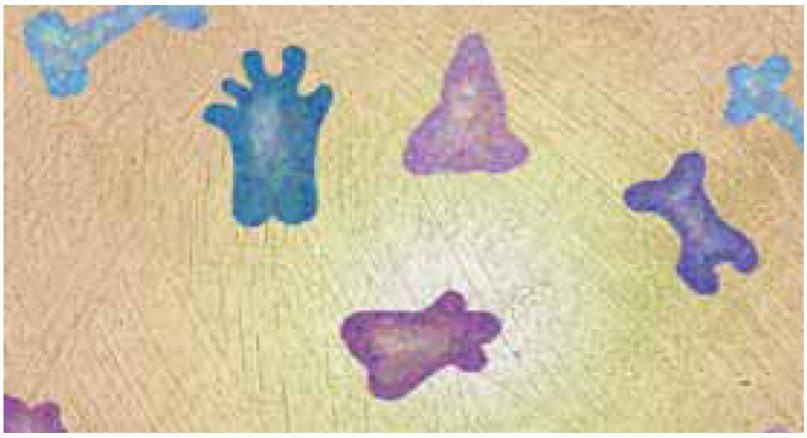
Disadvantages:

• May very rarely revert to its virulent form and cause disease. Live vaccines cannot be given safely to immune suppressed individuals Administration of live attenuated vaccines to people with impaired immune function can cause serious illness or death in the vaccine recipient.

4.1.3.SUBUNIT VACCINES

Subunit vaccines contain purified antigens instead of whole organisms. Such a preparation consists of only those antigens that elicit protective immunity. Subunit vaccines are composed of toxoids, sub cellular fragments, or surface antigens. Administration of whole organism, as in case of pertussis was found unfavorable immune reactions resulting in severe side effects. The effectiveness of subunit vaccines in increased by giving them in adjuvants.

Subunit vaccines contain just the antigens of the microbe that best stimulate the immune system. This image depicts antigens that have been separated from the rest of the microbe for use in a subunit vaccine.



Advantages:

• They can safely be given to immunosuppressed people

• They are less likely to induce side effects.

Disadvantages:

• Antigens may not retain their native conformation, so that antibodies produced against the subunit may notrecognize the same protein on the pathogen surface.

• Isolated protein does not stimulate the immune system as well as a whole organism vaccine.

4.1.4.PEPTIDE VACCINE

Peptide vaccine consists of those peptides from the microbial antigen that stimulates protective immunity. Synthetic peptides are produced by automated machines rather than by microorganisms. Peptide immunogenicity can be increased by giving them in ISCOMS, lipid micelles that transport the peptides directly into the cytoplasm of dendritic cells for presentation on Class I MHC. Injected peptides, which are much smaller than the original virus protein, induce an IgG response. Example: spf66 anti-malarial vaccine

Advantages:

• If the peptide that induces protective immunity is identified, it can be synthesized easily on a large scale.

• It is safe and can be administered to immune deficient and pregnant individuals.

Disadvantage:

• Poor antigenicity. Peptide fragments do not stimulate the immune system as well as a whole organism vaccine.

• Since peptides are closely associated with HLA alleles, some peptides may not be universally effective at inducing protective immunity.

4.1.5.CONJUGATE VACCINES

Conjugate vaccines are primarily developed against capsulated bacteria. While the purified capsular antigen can act as subunit vaccine, they stimulate only humoral immunity. Polysaccharide antigens are T independent, they generate short-lived immunity. Immunity to these organisms requires opsonizing antibodies. Infants cannot mount good T-independent responses to polysaccharide antigens. By covalently linking the polysaccharides to protein carriers, they are converted into T-dependent antigens and protective immunity is induced.

Examples: *Haemophilus influenzae* HiB polysaccharide is complexed with diphtheria toxoid. Tetramune vaccine, which combines the tetanus and diphtheria toxoids, whole-cell pertussis vaccine, and *H. influenzae* type bconjugate vaccine.

4.6.RECOMBINANT VACCINES

The vaccines are produced using recombinant DNA technology or genetic engineering. Recombinant vaccines are those in which genes for desired antigens of a microbe are inserted into a vector. Different strategies are:

• Using the engineered vector (e.g., Vaccine a virus) that is expressing desired antigen as a vaccine

• The engineered vector (e.g., yeast) is made to express the antigen, such is vector is grown and the antigen is purified and injected as a subunit vaccine. Other expression vectors include the bacteria *Escherichia coli*, mutant Salmonella spp., and BCG.

• Introduction of a mutation by deleting a portion of DNA such that they are unlikely to revert can create an attenuated live vaccine.

• Live attenuated vaccines can also be produced by reassertment of genomes of virulent and a virulent strains.

• Genes coding for significant antigens are introduced into plants, such that the fruits produced bear foreign antigens. This is edible vaccine and is still in experimental stage.

Examples:

• Hepatitis B Virus (HBV) vaccine is a recombinant subunit vaccine.

• Vaccinia virus may be engineered to express protein antigens of HIV, rabies etc

• B subunit of cholera toxin, the B subunit of heat-labile *E. coli* enterotoxin (LT),

• *Salmonella typhimurium* engineered to express antigens of *Vibrio cholerae.*

• Bacille Calmette-Guérin vaccine strain engineered to express genes of HIV-1.

• Reassortment of genomes between human and avian strains to create Influenza vaccine. Human and swine strains to create Rotavirus vaccine.

Advantages:

• Those vectors that are not only safe but also easy to grow and store can be chosen.

• Antigens which do not elicit protective immunity or which elicit damaging responses can be eliminated fromthe vaccine. Example Cholera toxin A can be safely removed from cholera toxin.

Disadvantages:

• Since the genes for the desired antigens must be located, cloned, and expressed efficiently in the new vector, the cost of production is high.

4.1.7.DNA VACCINES

These vaccines are still in experimental stage. Like recombinant vaccines, genes for the desired antigens are located and cloned. The DNA is injected into the muscle of the animal being vaccinated, usually with a "gene gun"that uses compressed gas to blow the DNA into the muscle cells. DNA can be introduced into tissues by bombarding the skin with DNA-coated gold particles. It is also possible to introduce DNA into nasal tissue in nose drops. Some muscle cells express the pathogen DNA to stimulate the immune system. DNA vaccines have induced both humoral and cellular immunity.

Advantages:

• DNA is very stable, it resists extreme temperature and hence storage and transport are easy.

• A DNA sequence can be changed easily in the laboratory.

• The inserted DNA does not replicate and encodes only the proteins of interest.

• There is no protein component and so there will be no immune response against the vector itself.

Disadvantages:

• Potential integration of DNA into host genome leading to insertional mutagenesis.

• Induction of autoimmune responses: anti-DNA antibodies may be produced against introduced DNA.

• Induction of immunologic tolerance: The expression of the antigen in the host may lead to specific nonresponsiveness to that antigen.

4.1.8.ANTI-IDIOTYPIC VACCINE

An antigen binding site in an antibody (paratope) is a reflection of the three-dimensional structure of part of the antigen (epitope). This unique amino acid structure in the antibody is known as the idiotype, which can be considered as a mirror of the epitope in the antigen. Antibodies can be raised against the idiotype by injecting the antibody into another animal. This anti-idiotype antibody mimics part of the three dimensional structure of the antigen. This can be used as a vaccine. When the anti-idiotype antibody is injected into a vaccinee, antibodies (antianti-idiotype antiobodies) are formed that recognize a structure similar to part of the virus and might potentially neutralize the virus.

Advantage:

Antibodies against potentially significant antigen can be produced.

Disadvantage:

Only humoral immunity is produced. There is no cellular immunity and poor memory. Identification and preparation of idiotypes is labor intensive and difficult.

• There is no protein component and so there will be no immune response against the vector itself.

• Because of the way the antigen is presented, there is a cell-mediated response that may be directed against any antigen in the pathogen.

4.2.Vaccines of the Future

Aside from the “ouch factor,” vaccines delivered through a needle in the arm or elsewhere have some shortcomings. The needles used to inject vaccines must be kept sterile, for example, which is difficult in some settings. Also, injections usually must be administered by trained personnel, and injecting many people quickly as would be necessary in case of a widespread outbreak is not easy. For these reasons, scientists are investigating new ways to deliver vaccines. Although still a long way off, edible vaccines would make it cheaper and easier to immunize people against diseases, especially in developing countries where storing and administering vaccines is often difficult. Scientists have shown that potatoes genetically engineered to produce an *Escherichia coli* antigen safely triggered an immune response to this bacterium in people who ate small pieces of the potatoes. Similarly, a potato-based vaccine against hepatitis B virus yielded promising results in an early stage of human testing. Researchers have also modified bananas to protect against norovirus, a common cause of diarrhea, and have created a food-based vaccine containing a protein from respiratory syncytial virus, which can cause serious respiratory illness, especially in young children. Recently, research into plant-based vaccines has focused less on food crops and more on genetically modifying plants that are not normally eaten. Vaccine components are produced in the leaves, which are then freeze-dried, ground up, and placed in gelatin capsules. Another novel way being investigated to deliver vaccines simply is through a thin skin patch. Skin is one of our best defenses against infection. But it also includes large numbers of certain immune system cells, called dendritic cells, which can react to a vaccine placed on the skin. Skin patch vaccines are being tested for a range of diseases, including travelers’ diarrhea, tetanus, anthrax, and seasonal flu. In 2003, the Food and Drug Administration (FDA) licensed a new vaccine for seasonal influenza that’s delivered as spray into the nose. The vaccine, created with National Institute of Allergy and Infectious Diseases (NIAID) support, is made from a live, attenuated flu virus. FDA has approved it for healthy people 2 to 49 years old. The vaccine is being tested to see if it can eventually be approved for use in older people and in children under 2 as well. Delivering this vaccine as a nasal mist not only eliminates the needle making it easier to give to children but it also closely mimics how the flu virus actually enters your body, which may produce a better immune response.

Chapter Five:Common Vaccine

1.Cholera	11.Mumps
2.Diphtheria	12.Pneumonia
3.Tetanus	13.Polio
4.Hameophilus Influenza Type B	14.Rabies
5.Hepatitis A	15.Rotavirus
6.Hepatitis B	16.Rubella
7.Human papilloma	17.TB
8.Seasonal Influenza	18.Typhoid Fever
9.Measles	19.Yellow Fever
10.Meningococcal	20.Pertusis

5.1.CHOLERA

Cause: Vibrio cholerae bacteria of serogroups O1 and O139.

Transmission: Infection occurs through ingestion of food or water contaminated directly or indirectly by faeces or vomit us of inected individuals. Cholera affects only humans; there is no insect vector or animal reservoir host

.**Nature of the disease:** An acute enteric disease varying in severity. Most infections are asymptomatic (i.e. do not cause any illness). In mild cases, acute watery diarrhoea occurs without other symptoms. In severe cases, there is sudden onset of profuse watery diarrhoea with nausea and vomiting and rapid development of dehydration. In severe untreated cases, death may occur within a few hours due to dehydration leading to circulatory collapse.

Geographical distribution : Cholera occurs mainly in low-income countries with inadequate sanitation and lack of clean drinking-water and in war-torn areas where the infrastructure may have broken down. Many developing countries are affected, particularly in Africa and Asia and, to a lesser extent, in central and South America.

Risk for travelers: The risk for most travellers is very low, even in countries where cholera epidemics occur, provided that simple precautions are taken. However, humanitarian relief workers in disaster areas and refugee camps may be at risk.

Vaccine: A vaccine consisting of killed whole-cell V. cholerae O1 in combination with a recombinant B-subunit of cholera toxin (WC/rBS) has been marketed since the early 1990s. This killed vaccine is well tolerated and confers high-level (85–90%) protection for 6 months after the second immunization in all vaccines aged more than 2 years. Three years after immunization the level of protection is still about 50% in vaccines who were 5 years or older at the time of vaccination. Primary immunization consists of two oral doses 7–14 days apart for adults and children aged 6 years and over. For children aged 2–5 years, three doses are recommended. Intake of food and drinks should be avoided 1 hour before 6 and after vaccination. If the second dose is delayed for more than 6 weeks, vaccination should be restarted.

5.2.DIPHTHERIA

Cause: Toxigenic *Corynebacterium diphtheriae (C. diphtheria)* and occasionally, toxigenic *Corynebacterium ulcerans (C. ulcerans).*

Transmission: *C. diphtheriae* typically resides in the upper respiratory tract and is transmitted from person to person through droplets and close physical contact. Transmission is facilitated by crowding and poor socioeconomic conditions. A cutaneous form of diphtheria caused by *C. ulcerans* is common in tropical countries. This bacterium is easily transmitted by close contact. Chronic carriage of *C. diphtheria* and *C. ulcerans* occurs frequently.

Nature of the disease: Diphtheria is caused by a potent bacterial toxin that can produce obstructive pseudo-membranes in the upper respiratory tract (croup) or damage to the myocardium and other tissues. Although asymptomatic or mild infections are most common, untreated diphtheria may be severe and sometimes fatal. *C. ulcerans* can cause respiratory or cutaneous diphtheria in nonimmunized individuals and cutaneous, mostly non-toxic lesions even in fully vaccinated individuals.

Geographical distribution: Diphtheria is found worldwide, although it is not common in industrialized countries because of long-standing routine use of diphtheria/tetanus/pertussis (DTP) vaccine. Large epidemics occurred in several east European countries in the 1990s.

Risk for travelers: Non-immunized or incompletely immunized travellers have occasionally contracted diphtheria when visiting endemic areas. The disease occurs more frequently in parts of the world where DTP coverage is low.

Vaccine: All travellers should be vaccinated according to national recommendations. Vaccination against diphtheria is usually given as triple vaccine DTP or DTaP (diphtheria/tetanus/acellular pertussis). After the initial course of three such doses, additional doses may be given as DT to children <7 years of age; individuals ≥7 years of age should receive a vaccine with reduced diphtheria content (Td). Since both tetanus toxoid (see below) and diphtheria toxoid can reasonably be given on a booster basis about every 10 years, there is no reason to use monovalent diphtheria vaccine. In some countries, adult boosters that contain TdaP are being introduced.

5.3.TETANUS

Cause: The bacterium *Clostridium tetani (C. tetani)*

Transmission: Tetanus is acquired through exposure to the spores of *C. tetani* which are present in soil worldwide. The disease is not communicable.

Nature of the disease : The disease is caused by the action of a potent bacterial neurotoxin released from wounds contaminated by *C. tetani*. Clinical symptoms

are muscle spasms, initially of the muscles of mastication causing trismus or "lockjaw". Trismus can be followed by sustained spasm of the back muscles (opisthotonus) and by spasms of other muscles. 9 Generalized, tetanic seizures will ultimately lead to death unless intense supportive treatment is rapidly initiated.

Geographical distribution Wounds can become infected with the spores of *C. tetani* anywhere in the world.

Risk for travelers: Every traveller should be fully vaccinated against tetanus. Almost any form of injury, from a simple laceration to a motor-vehicle accident,

can expose the individual to the spores.

Vaccine : Tetanus vaccine is available as monovalent tetanus toxoid (TT), in bivalent combination with diphtheria toxoid (DT) or low-dose diphtheria toxoid (Td), or as trivalent vaccine that also includes whole-cell (wP) or acellular (aP) pertussis vaccine. In some countries, combination vaccines with hepatitis B, *Haemophilus influenzae* type b and/or IPV exist. Vaccines containing DT are used for children under 7 years of age and Td-containing vaccines for those aged 7 years and over. Vaccine combinations containing diphtheria toxoid (D or d) and tetanus toxoid, rather than tetanus toxoid alone, should be used when immunization against tetanus is indicated. A childhood immunization schedule of 5 doses is recommended. The primary series of 3 doses of DTP (DTwP or DTaP) should be given in infancy, with a booster dose of a tetanus toxoid-containing vaccine ideally at age 4–7 years and another booster in adolescence, e.g. at age 12–15 years. Those who have received the primary series plus two booster doses, the last of which given in early adulthood, are unlikely to require further doses. All travellers should be up to date with the vaccine before departure. The type of tetanus prophylaxis that is required following injury depends on the. nature of the lesion and the history of previous immunization.

5.4.HAEMOPHILUS INFLUENZA TYPE B

Cause The bacterium *Haemophilus influenzae* type b (Hib).

Transmission: Respiratory droplets.

Nature of the disease: *Haemophilus influenzae* type b is a common cause of pneumonia and meningitis and of a number of other serious and potentially life threatening conditions, including epiglottitis, osteomyelitis, septic arthritis and septicaemia. Rarely occurring in infants under 3 months of age or children after the age of 5 years, the disease burden is highest between 4 and 18 months of age. Hib is the dominant cause of sporadic (non-epidemic) bacterial meningitis in this age group, and is frequently associated with severe neurological sequelae despite prompt and adequate antibiotic treatment.

Geographical distribution: It is estimated that each year Hib causes 7–8 million cases of pneumonia and hundreds of thousands of deaths, mainly in 11 developing countries. The disease has practically disappeared in countries where routine Hib vaccination of children is carried out.

Risk for travellers All unprotected children are at risk, at least up to the age of 5 years.

Vaccine Vaccination against Hib is recommended for all children over 6 weeks and up to 2 years of age. Infants 6 weeks – 12 months of age should receive a primary series of 3 doses, whereas one dose is sufficient in previously unvaccinated children aged 12 months or more. The vaccine is often given in fixed combinations with one or more other vaccines, such as DTP, hepatitis B vaccine or IPV, in routine immunization programmes.

5.5.HEPATITIS A

Cause: Hepatitis A virus (HAV), a member of the *Picornaviridae* family.

Transmission: The virus is acquired through close contact with infected individuals or through faecally contaminated food or drinking-water. There is no insect vector or animal reservoir.

Nature of the disease: Acute viral hepatitis is characterized by abrupt onset of fever, malaise, nausea and abdominal discomfort, followed by jaundice a few days later. Infection in very young children is usually mild or asymptomatic whereas in older children symptomatic disease is common. The disease is often more severe in adults and full recovery may take several months. Case-fatality is greater than 2% for those over 40 years of age and about 4% for those aged 60 years, or more.

Geographical distribution: Worldwide, but most common in areas where sanitary conditions are poor (see map).

Risk for travelers: Non-immune travellers to developing countries are at significant risk of infection, in particular in settings with poor food and drinking water control and poor sanitation. People born and raised in developing countries, and those born before 1945 in industrialized countries, have usually been HAV infected in childhood and are likely to be immune.

Precautions: Avoid or boil potentially contaminated food and water. Short-term protection through injection of human immune globulin is gradually being replaced worldwide by hepatitis A vaccination.

Vaccine: Two types of HAV vaccines are currently available internationally:

1) Formaldehyde-inactivated vaccines: Inactivated HAV vaccines are used in most countries. Monovalent inactivated HAV vaccines are available in paediatric dose (0.5 ml) for children aged >1 year to 15 years, and in adult dose (1 ml).

2) Live attenuated vaccines (based on H2 or LA-1 HAV strains): These vaccines are manufactured and used mainly in China and sporadically in the private sector in India.

1. Inactivated hepatitis A vaccines are safe and highly effective. Traditionally, a two-dose schedule is recommended, particularly in travellers at substantial risk of contracting hepatitis A and 12 immunocomprised individual.

5.6.HEPATITIS B

Cause: Hepatitis B virus (HBV), belonging to the *Hepadnaviridae* family.

Transmission: Infection is transmitted from person to person by contact with infected body fluids. Sexual contact is an important mode of transmission, but infection is also transmitted by transfusion of contaminated blood or blood products, or by use of contaminated needles or syringes for injections.

Nature of the disease: Most acute HBV infections are asymptomatic or cause mild symptoms, which are often unrecognized. Symptomatic acute disease occurs in about 1% of perinatally infected individuals, in 10% of children infected between 1 and 5 years of age, and in about 30% of individuals infected after the age of 5 years. Clinical acute hepatitis B has a gradual onset, with anorexia, abdominal discomfort, nausea, vomiting, arthralgia and rash, followed by the development of jaundice in some cases. In adults, about 1% of cases are fatal.

Geographical distribution: The endemicity of HBV in a population is described by the prevalence of HBsAg, an HBV-specific component found in the blood (and other body fluids) in both acute and chronic stages of the infection. HBV is found worldwide, but with differing levels of endemicity. The majority of the world's population live in countries where the prevalence of HBsAg of in the general population is high (≥8%) or intermediate (2-7%). In certain areas of North America, northern and western Europe, the southern cone of South America, Australia and New Zealand, prevalence of chronic HBV infection is relatively low

Risk for travelers: The risk depends on

(1) the prevalence of HBV infection in the country or area of destination,

(2) the extent of direct contact with blood or body fluids or of sexual contact with potentially infected individuals.

Vaccine: Hepatitis B vaccine is produced by recombinant DNA technology,

most commonly in yeast. The complete vaccination series consists of three doses of vaccine; the first two doses are usually given 1 month apart, with the third dose 1–12 months later.

5.7.HUMAN PAPILLOMA

Cause Human papillomavirus (HPV), belonging to the *Papillomaviridae* family.

Transmission Genital HPV infections are transmitted primarily by sexual contact, predominantly but not exclusively through penetrative intercourse. HPV is highly transmissible, and most sexually active men and women will acquire an HPV infection at some time in their lives.

Nature of the disease: Whereas most HPV infections are transient and benign, persistent genital infection with certain viral genotypes can lead to the development of anogenital precancers and cancers. Diseases caused by HPV include cancers of the cervix, vagina, vulva, penis and anus; a subset of head and neck cancers; anogenital warts; and recurrent respiratory papillomatosis.

Geographical distribution: HPV is very common all over the world. In 2005, there were an estimated 500 000 cases of cervical cancer worldwide and 260 000
related deaths. Cervical cancer incidence rates vary from 1 to 50 per 100 000 females; rates are highest in Latin America and the Caribbean, sub-Saharan Africa, Melanesia, and south-central and south-east Asia.

Risk for travelers: Transmission of HPV occurs most commonly through sexual
activity; see precautions under “HIV/AIDS and other sexually transmitted infections

Vaccines: Since 2006, two HPV vaccines have been licensed; one vaccine targets four and the other two HPV genotypes. Both vaccines are designed to protect against about 70% of cervical cancer cases worldwide (the 4-valent vaccine also protects against genital warts). Both vaccines are intended to be administered to females before the onset of sexual activity – that is, before first exposure to HPV infection. Most countries that have licensed these vaccines, recommend their use in girls aged 10–14 years. In some countries the quadrivalent vaccine is offered to girls as young as 9 years. Some national programmes also recommend routine - or temporary catchup vaccination - of older adolescent females and young women.The complete series of quadrivalent vaccine is administered at day 0; 2 months; and 6 months. The bivalent vaccine is administered at day 0; 1 month; and 6 months. Repeating previous doses is not necessary if the 3-dose programme has been interrupted. Booster doses are currently not recommended.

5.8.SEASONAL INFLUENZA

Cause: Influenza viruses belonging to the family *Orthomyxoviridae*. The influenza viruses are classified into types A, B and C on the basis of their nucleoproteins. Only types A and B cause human disease of 18 any concern. The subtypes of influenza A viruses are determined by envelope glycoproteins possessing either haemagglutinin (HA) or neuraminidase (NA) activity. High mutation rates and frequent genetic reassortments of these viruses contribute to great variability of the HA and NA antigens. The majority of the currently identified 17 HA and 10 NA subtypes of influenza A viruses are maintained in wild, aquatic bird populations. Humans are generally infected by viruses of the subtypes H1, H2 or H3, and N1 or N2. Minor point mutations causing small changes ("antigenic drift") occur relatively often

Transmission: Respiratory transmission occurs mainly by droplets disseminated by unprotected coughs and sneezes. Airborne transmission of influenza viruses occurs particularly in crowded spaces. Hand contamination followed by direct mucosal inoculation of virus is another possible source of transmission.

Nature of the disease: Influenza is an acute respiratory infection of varying severity, ranging from asymptomatic infection to fatal disease

Geographical distribution: Influenza occurs all over the world, with an annual global attack rate estimated at 5–10% in adults and 20–30% in children. In temperate regions, influenza is a seasonal disease occurring typically in winter

months: it affects the northern hemisphere from November to April and the southern hemisphere from April to September.

Risk for travelers: Travellers, like local residents, are at risk during the influenza season. In addition, groups of travellers (e.g. on cruise ships) that include individuals from areas affected by seasonal influenza may experience out-of season outbreaks.

Vaccine: Both trivalent inactivated vaccines and trivalent (or quadrivalent) live

attenuated influenza vaccines are available. There are 3 types of trivalent inactivated vaccines: whole virus vaccines, split virus vaccines, and subunit vaccines. In most countries, whole virus vaccines have been replaced by less reactogenic split virus and subunit vaccines. Inactivated trivalent vaccines are the only influenza vaccines licensed for vaccination of children <2 years of age, for persons aged ≥ 50 years, and for pregnant women.

5.9.MEASLES

Cause: Measles virus, genus *Morbillivirus*, and family Paramyxoviridae.

Transmission Transmission, which is primarily by airborne respiratory droplets,

during the late winter and early spring in temperate climates and after the rainy season in tropical climates.

Nature of the disease: Measles is a highly contagious infection; before vaccines became available, this disease had affected most people by the time of adolescence. Epidemics may still occur every 2 or 3 years in areas where there is low vaccination coverage. In countries where measles has been largely eliminated, cases imported from other countries remain an important continuing source of infection. In 2009, worldwide measles vaccination coverage had reached 82%, and between 2000 and 2008 the estimated annual number of deaths from measles dropped from 733 000 to 164 000. The classical signs and symptoms of measles include fevers, cough, nasal congestion, and rashes. Common complications include bacterial middle-ear infection and pneumonia

Geographical distribution: In the pre-vaccine era, measles outbreaks occurred all over the world. Following the introduction of large-scale measles immunization, indigenous transmission has virtually stopped in the Americas and in many industrialized countries worldwide.

Risk for travelers: Measles is still common in many countries and travel in densely populated areas may favour transmission. Travellers who are not fully immunized against measles are at risk. Special attention must be paid to all children and adolescent/young adult travellers who have not received two doses of measles vaccine.

Vaccine: A number of live, attenuated measles vaccines are currently available,either as monovalent vaccine or as measles-containing vaccine combinations with one or more of rubella (R), mumps (M), and varicella vaccines. The measles/ mumps/ rubella (MMR) or measles/rubella (MR) vaccine is given in many countries instead of monovalent measles vaccine. The measles vaccines that are now internationally available are safe and effective and may be used interchangeably in immunization programmes. Every child should receive two doses of measles vaccine. The second dose may be given as early as 1 month following the first, depending on the local programmatic and epidemiological situation. For infants

5.10.MENIGOCOCCAL DISEASE

Cause: *Neisseria meningitides* bacteria, in most cases serogroups A, B and C, less commonly, Y and X. Serogroup W-135 is of increasing concern.

Transmission: Transmission occurs by direct person-to-person contact and through respiratory droplets from patients or asymptomatic meningococcal carriers. Humans are the only reservoir.

Nature of the disease: As a rule, endemic disease occurs primarily in children and adolescents, with highest attack rates in infants aged 3–12 months, whereas in meningococcal epidemics, rates may rise also in older children and young adults.Meningococcal meningitis has a sudden onset of intense headache, fever, nausea, vomiting, photophobia and stiff neck, plus various neurological signs. The disease is fatal in 5–10% of cases even with prompt antimicrobial treatment in good health care facilities. Among individuals who survive, up to 20% have permanent neurological sequelae. Meningococcal septicaemia, in which there is rapid dissemination of bacteria in the blood-stream, is a less common form of meningococcal disease, characterized by circulatory collapse, haemorrhagic skin rash and high fatality rate.

Geographical distribution: Sporadic cases are found worldwide. In temperate zones, most cases occur in the winter months. Localized outbreaks occur in enclosed crowded spaces (e.g. dormitories, military barracks). In the “meningitis belt” of sub-Saharan Africa, a zone stretching across the continent from Senegal to Ethiopia, large outbreaks and epidemics take place during the dry season (November to June). Recent reports of group Y meningococcal disease in the United States.

Risk for travelers: The risk of meningococcal disease in travellers is generally low. Those travelling to industrialized countries may be exposed to sporadic cases mostly of A, B or C. Long-term travellers living in close contact with the indigenous population may be at greater risk of infection. Pilgrims visiting Mecca for the Hajj or Umrah are at particular risk.

Vaccines: *Polysaccharide vaccines* Internationally marketed meningococcal polysaccharide vaccines are bivalent (A and C), trivalent (A, C and W-135) or tetravalent (A, C, Y and W-135). The vaccines are purified, heat-stable, lyophilized capsular polysaccharides from meningococci of the respective sero groups. Following one dose, both group A and group C vaccine have documented short time efficacy level of 80%-100% in order children and adults.

5.11.MUMPS

Cause: Mumps virus, genus *Rubulavirus*, family *Paramyxoviridae*.

Transmission: Humans are the only known natural host for mumps virus, which is spread via direct contact or by airborne droplets from the upper respiratory tract of infected individuals.

Nature of the disease: Mumps (*parotitis epidemica*) is a viral infection of humans, primarily affecting the salivary glands. Although it is mostly a mild childhood disease, with peak incidence occurring among those aged 5–9 years, the mumps virus may also affect adults, among whom complications such as meningitis and orchitis are relatively more common. Encephalitis and permanent neurological sequelae are rare complications.

Geographical distribution: Except in countries with high coverage of mumps-containing vaccines, the annual mumps incidence in most parts of the world is in the range of 100–1000 per 100 000 population, with epidemic peaks every 2–5 years.

Risk for travelers: Travellers who are not fully immunized against mumps are at risk.

Vaccine: The mumps vaccine is usually given in combination with measles and rubella vaccine (MMR). The attenuated strains of mumps virus that are currently used for the production of live mumps vaccines are all considered to be safe and efficacious. In order to avoid possible interference with persistent maternal antibodies, the first of the two recommended doses of the vaccine is usually given at 12–18 months of age. A single dose of mumps vaccine, either as single antigen or in combination, has a protective efficacy of 90–96%.The second dose provides protection to most individuals who did not respond to the first and should be given after a minimum interval of 1 month. In some countries the second dose is given at the age of 4–6 years.

5.12.PNEUMONIA

Cause: Many serotypes of the bacterium *Streptococcus pneumoniae*.

Transmission: Infection is acquired mainly through pneumococci contained in respiratory droplets. There are many healthy, asymptomatic carriers of the bacteria, but no animal reservoir or insect vector.

Nature of the disease: Pneumonia with empyema and/or bacteraemia, febrile bacteraemia and meningitis are the commonest manifestations of invasive pneumococcal infection. Pneumococci are a frequent cause of non-bacteraemic pneumonia. In developing countries, non-bacteraemic pneumonia causes the majority of pneumococcal deaths in children. Middle-ear infections, sinusitis and bronchitis are non-invasive and less severe manifestations of pneumococcal infection, but are considerably more common. Several chronic conditions predispose to serious pneumococcal disease.

Geographical distribution: Pneumococcal infection is a major cause of morbidity and mortality worldwide. In 2005, WHO estimated that 1.6 million deaths were caused by this agent annually; this estimate included the deaths of 0.7–1 million children aged under 5 years. Most of these deaths occurred in poor countries and included a disproportionate number of children under the age of 2 years. In Europe and the USA, S. pneumoniae is the most common cause of community acquired bacterial pneumonia in adults. In these regions, the annual incidence of invasive pneumococcal disease ranges from 10 to 100 cases per 100 000 population.

Risk for travelers: While travel itself does not normally increase the risk of acquiring pneumococcal disease, access to optimal health care may be limited during travel, increasing the risk of a poor outcome should disease occur. Thus, before undertaking travel to countries with limited medical resources, vaccination against invasive pneumococcal disease is advisable for children <2 years of age and for children and adults considered to be at particular risk of serious disease. Conditions predisposing to complications of pneumococcal infections include sickle-cell disease and other haemoglobinopathies, chronic renal failure, chronic liver disease, immune suppression after organ transplantation, asplenia and dysfunctional spleen, leaks of cerebrospinal fluid, diabetes mellitus and HIV infection.

5.13.POLIO

Cause Poliovirus types 1, 2 and 3 (three closely related enteroviruses).

Transmission Polio viruses are spread predominantly by the faecal–oral route. In settings with high standards of hygiene, the oral–oral route of transmission may also be common.

Nature of the disease Poliomyelitis, also known as polio or infantile paralysis, is a disease of the central nervous system. Following primary asymptomatic infection of the alimentary tract, fewer than 1% develop paralytic disease. In developing countries, 65–75% of cases occur in children under 3 years of age and 95% in children under 5 years of age. The resulting paralysis is permanent, although some recovery of function is possible. There is no cure.

Geographical distribution: Significant progress has been made towards global eradication of poliomyelitis. As of August 2012, polio remains endemic in three countries Afghanistan, Nigeria and Pakistan and has reestablished transmission in three countries which were previously polio-free (Angola, Chad and the Democratic Republic of the Congo). Several more countries had ongoing outbreaks in 2011 due to importations of poliovirus.

Risk for travelers: Until the disease has been certified as eradicated globally, the risks of acquiring polio (for travellers to infected areas) and of reinfection of polio-free areas (by travellers from infected areas) remain. All travellers to and from poliovirus-infected areas should be adequately vaccinated. Updates on currently or recently infected countries can be found.

Vaccines: Both orally administered, live attenuated polio vaccines (OPV) and inactivated polio vaccines (IPV) for intramuscular (or subcutaneous) injection are widely used internationally. OPV has been the vaccine of choice for controlling poliomyelitis in many countries, and for the global polio eradication initiative, because of the ease of oral administration, its superiority in conferring intestinal immunity, and its low cost. The only, extremely rare, adverse event associated with OPV use is vaccine-associated paralytic poliomyelitis (VAPP), which may occur in vaccine recipients or their contacts. The overall risk of VAPP is estimated at around 1 case per 2.4 million doses administered. As long as transmission of wild poliovirus has not been interrupted globally, WHO recommends that OPV should remain the vaccine of choice for routine infant immunization in most countries.

5.14.RABIES

Cause Lyssavirus of the family *Rhabdoviridae*.

Transmission Rabies is a zoonotic disease affecting a wide range of domestic and wild mammals, including bats. The virus is present primarily in the saliva and infection of humans usually occurs through the bite of an infected animal, usually a dog, which may not show signs of rabies. Transmission may occasionally occur also through other contact with a rabid animal, for example following a penetrating scratch with bleeding, or through licking of broken skin and mucosa. Laboratory confirmed person-to-person transmission other than via organ transplant has not been reported.

Nature of the disease Rabies is an acute viral encephalomyelitis, which is almost invariably fatal. The initial signs include a sense of apprehension, headache, fever, malaise and sensory changes around the site of the animal bite. Excitability, hallucinations and abnormal fear of drafts of air (aerophobia) are common, followed in some cases by fear of water (hydrophobia) due to spasms of the swallowing muscles, progressing to delirium, convulsions and death a few days after onset. A less common form, paralytic rabies, is characterized by paralysis and loss of sensation, weakness and pain.

Geographical distribution: Rabies is present in mammals in most parts of the world. Most of the estimated 55 000 human rabies deaths per year occur in Africa and Asia..

Risk for travelers: The risk to travellers in areas where rabies is proportional to the probability of contact with potentially rabid mammals. In most developing countries, the estimated ratio of dogs, both owned and ownerless, to humans is 1:10 and an average 100 suspected rabid dog bites per 100 000 inhabitants are reported annually. As rabies is a lethal disease, medical advice should be sought immediately at a competent medical centre – ideally, the rabies treatment centre of a major city hospital.

Vaccine: Vaccination against rabies is used in two distinct situations:

- to protect those who are at risk of exposure to rabies, i.e. pre exposure vaccination;
- to prevent the development of clinical rabies after exposure has occurred, usually following the bite of an animal suspected of having rabies, i.e. post-exposure prophylaxis.

The vaccines used for pre-exposure and post-exposure vaccination are the same, but the immunization schedule differs.

5.15.ROTAVIRUS

Cause: Viruses belonging to the family of *Reoviridae.*

Transmission: Transmission is primarily by the faecal oral route, directly from person to person, or indirectly via contaminated fomites. A respiratory mode of transmission has also been proposed.

Nature of the disease: Rotavirus causes an acute gastroenteritis in infants and young children and is associated with profuse watery diarrhoea, projectile vomiting and fever. Rapid dehydration requiring rehydration therapy can occur, especially in very young infants. The virus replicates in the enterocytes of the small intestine, causing extensive damage to the microvilli and resulting in malabsorption and loss of fluids and electrolytes.

Geographical distribution: Rotaviruses are found worldwide. They are the leading cause of severe, dehydrating diarrhoea in children under 5 years globally:

outpatient visits are estimated at more than 25 million and hospitalizations attributable to rotavirus infections at more than 2 million each year. The World Health Organization estimates that in 2008 453 000 (420 000 - 494 000) child deaths occurred due to rotavirus gastroenteritis world-wide. Fatal outcomes occur

predominantly in low-income countries. In temperate climates, the incidence of rotavirus gastroenteritis typically peaks during the winter season, whereas in tropical settings this type of gastroenteritis occurs year round. Re infection of older children and adults is common, although re infections are usually sub-clinical.

Risk for travelers: The risk for adult travellers is negligible since most individuals will have good immunity through repeated exposures early in life. Children under the age of 5 years are at risk.

Vaccines: Two live, attenuated, oral rotavirus vaccines are internationally licensed and routine childhood vaccination has been initiated in a number of countries. The clinical efficacy of the rotavirus vaccines has been demonstrated in most parts of the world. WHO recommends the inclusion of rotavirus vaccination in all national immunization programmes, particularly in countries at high risk of severe disease and fatal outcomes. Rotarix vaccine should be administered orally in a 2-dose schedule at the time of the first and second doses of DTP and with an interval of 4 weeks between the doses.

5.16.RUBELLA

Cause: Rubella virus, a togavirus of the genus *Rubivirus*.

Transmission: Rubella virus is transmitted by the respiratory route and the virus replicates in the nasopharyngeal mucosa and local lymph nodes. Humans are the only known host.

Nature of the disease: Acquired rubella is characterized by a transient, erythematous rash, conjunctivitis, coryza, postauricular and suboccipital

lymphadenopathy, low fever and nausea. Arthralgia and arthritis rarely occur in children, but may affect up to 70% of adults, particularly women. Haemorrhagic manifestations, Guillain_Barré syndrome and encephalitis are reported rarely. Serological studies have shown that 20-50% of all rubella infections are subclinical. Congenital rubella infection and congenital rubella syndrome (CRS) are caused by infection in early pregnancy. From just before conception and during the first 8_10 weeks of gestation, rubella infection may result in multiple fetal defects in up to 90% of cases and often causes miscarriage or stillbirth. Although the worldwide burden of CRS is not well characterized, it is estimated that more than 100 000 cases occur each year in developing countries alone.

Geographical distribution: Worldwide.

Risk for travelers: Travellers who are not immunized against rubella may be at risk when visiting countries where the vaccine coverage is suboptimal. Particular attention should be paid to ensuring protection of women who may become pregnant during the period of travel.

Vaccine: The internationally licensed rubella vaccines, based on the live attenuated RA 27/3 strain of the rubella virus and propagated in human diploid cells, have proved safe and efficacious, achieving 95– 100% protection, possibly lifelong, after just one dose. Following well-designed and well-implemented programmes using such vaccines, rubella and CRS have almost disappeared from many countries. Other attenuated vaccine strains are available in China and Japan.Rubella vaccine is commercially available in a monovalent form, in a bivalent combination with measles vaccine, as the trivalent measles/mumps/rubella (MMR) vaccine and in a few countries, also in a quadrivalent measles /mumps /rubella /varicella (MMRV) combination. Rubella-containing vaccines are usually administrated at 12–15 months of age but may be offered to children as young as 9 months. In principle, rubella vaccination of pregnant women should be avoided.

5.17.TB

Cause: The tubercle bacillus *Mycobacterium tuberculosis*.

Transmission In most cases, infection is transmitted by inhalation of M. tuberculosis-containing microscopic droplets originating from cases of active pulmonary tuberculosis

Nature of the disease Exposure to *M. tuberculosis* may lead to infection, but most infections do not lead to disease. The risk of developing disease following infection is generally 5–10% during the lifetime but may be increased by various factors, notably immunosuppression (e.g. advanced HIV infection). Multidrug resistance refers to strains of *M. tuberculosis* that are resistant to at least isoniazid and rifampicin (MDR-TB). The resistant strains do not differ from other strains in infectiousness, likelihood of causing disease, or general clinical effects; if they do cause disease, however, treatment is more difficult and the risk of death will be higher. Extensively drug-resistant TB (XDR-TB) is TB that is resistant to at least isoniazid and rifampin, to any fluoroquinolone and to at least one of the injectable second-line anti-TB drugs capreomycin, kanamycin and amikacin.

Geographical distribution Worldwide.

Risk for travellers :Most travellers are at low risk for TB. The risk for long-term (>3 months) travellers in a country with a higher incidence of TB than their own may be comparable to the risk for local residents. Living conditions, as well as duration of travel and purpose of travel, e.g. emergency relief, are important in determining the risk of infection: high-risk settings include impoverished communities, areas experiencing civil unrest or war, refugee areas, health facilities, prisons and shelters for the homeless. Individuals with HIV infection are at higher risk of TB.

Vaccine: All versions of the BCG vaccine are based on live, attenuated mycobacterial strains descended from the original, attenuated bacillus Calmette-Guérin. The vaccine is administered intradermally and can be given simultaneously with other childhood vaccines. BCG vaccine is contraindicated for individuals with severely impaired immunity and individuals with HIV infection. BCG vaccine is of very limited use for travellers. In the first year of life it provides good protection against severe forms of TB (military TB and meningitis). In countries with high TB prevalence, infants are generally immunized with a single dose of BGG as soon as after birth as possible.

5.18.TYPHOID FEVER

Cause: The typhoid bacillus *Salmonella typhi,* which infects humans only.

Paratyphoid and enteric fevers are caused by other species of *Salmonella*, which infect domestic animals as well as humans.

Transmission: The typhoid bacillus is transmitted by consumption of contaminated food or water. Occasionally, direct faecal oral transmission may occur. Shellfish taken from sewage-polluted areas are an important source of infection; transmission also occurs through eating raw fruit and vegetables fertilized by human excreta, and through ingestion of contaminated milk and milk products. Flies may cause human infection through transfer of the infectious agents to foods. Pollution of water sources may produce epidemics of typhoid fever, when large numbers of people use the same source of drinking-water.

Nature of the disease: Typhoid fever is a systemic disease of varying severity. Severe cases are characterized by gradual onset of fever, headache, malaise, anorexia and insomnia. Constipation is more common than diarrhea in adults and older children. Without treatment, some patients develop sustained fever, bradycardia, hepatosplenomegaly, abdominal symptoms and, occasionally, pneumonia. In white-skinned patients, pink spots, which fade on pressure, appear on the skin of the trunk in up to 20% of cases. In the third week, untreated cases may develop gastrointestinal and cerebral complications, which may prove fatal in up to 10–20% of the cases. The highest case-fatality rates are reported in children <4 years of age

Geographical distribution: There is a higher risk of typhoid fever in countries or areas with low standards of hygiene and water supply facilities.

Risk for travelers: The risk for travellers is generally low, except in parts of northern and western Africa, in southern Asia, in parts of Indonesia and in

Peru. Elsewhere, travellers are usually at risk only when exposed to low standards of hygiene.

Vaccine: Currently, two typhoid vaccines of demonstrated safety and efficacy

are available on the international market:1) The oral vaccine based on the live, attenuated mutant strain *of Salmonella typhi* Ty21a (Ty21a vaccine), is supplied in enteric coated capsules.

5.19.YELLOW FEVER:

Cause: Yellow fever virus (YFV), an arbovirus of the *Flavivirus* genus.

Transmission: Yellow fever occurs in urban and rural areas of Africa and central South America. In jungle and forest areas, monkeys are the main reservoir of infection, which is spread by mosquitoes from monkeyto monkey and, occasionally, to humans. In urban settings mosquitoes transmit the virus from human-to-human and introduction of infection into densely populated urban areas can lead to large epidemics of yellow fever. In Africa, an intermediate pattern of transmission is common in humid savannah regions where mosquitoes infect both monkeys and humans, causing localized outbreaks.

Nature of the disease: Although most infections are asymptomatic, some lead to an acute illness characterized by two phases. Initially, there is fever, muscular pain, headache, chills, anorexia, nausea and/or vomiting, often with bradycardia. About 15% of patients progress to a second phase after a few days, with resurgence of fever, development of jaundice, abdominal pain, vomiting and haemorrhagic manifestations; up to half of these patients die 10–14 days after the onset of illness.

Geographical distribution: In tropical areas of Africa and Central and South America (see maps) YFV transmission can occur at altitudes up to 2300 metres (in Africa, possibly higher). Countries or areas where the YFV is present far exceed those officially reported. Some countries may have no reported cases simply because of a high level of vaccine coverage against yellow fever, or because of poor surveillance. A revision of the risk classification of countries and areas recommended for yellow fever vaccination is reflected in this year's edition of IT&H

Risk for travellers Apart from areas of high yellow fever endemicity, YFV transmission may take place also in low-endemic areas if the traveller's itinerary implies heavy exposure to mosquitoes, for example during prolonged travel in rural areas.

General precautions: Avoid mosquito bites; the highest risk for YFV transmission is during the day and early evening.

Vaccine: The 17D vaccine, which is based on a live, attenuated viral strain, is the only commercially available yellow fever vaccine. It is given as a single subcutaneous (or IM injection) Yellow vaccines are highly effective approaching 100%.

5.20.PERTUSIS

Cause :The bacterium *Bordetella pertussis (B. pertussis*).

Transmission: *B. pertussis* is transmitted mainly by airborne droplets from the respiratory mucous membranes of infected individuals.

Nature of the disease: Pertussis (whooping cough) is a highly contagious acute bacterial disease involving the respiratory tract. Typical manifestations include several weeks of cough which gradually develop into severe coughing fits, ending in a characteristic "whoop", often with cyanosis and vomiting. In young infants, the cough may be absent and the disease may manifest with spells of apnoea. Although pertussis can occur at any age, most serious cases and fatalities are observed in early 10 infancy. Major complications include pneumonia, encephalitis and malnutrition (due to repeated vomiting).

Geographical distribution: WHO estimated that in 2008, about 16 million cases of pertussis occurred worldwide, 95% of which were in developing countries, and that some 195 000 patients died from this disease.

Risk for travelers:Unprotected young infants are at highest risk of severe pertussis, but older children, adolescents and adults may also contract the disease (often in mild and atypical form) if they are not fully immunized.Exposure to pertussis is more frequent in developing countries. All infants, including those who are HIV-positive, should be immunized against pertussis.

Vaccine: All travellers should be up to date with vaccination according to national recommendations. Both whole-cell (wP) and acellular (aP) pertussis vaccines provide excellent protection and are safe apart from minor adverse events. For several decades, Wp vaccines have been widely used in national childhood vaccination programmes; aP vaccines, which cause fewer adverse events but are more expensive, are now licensed in many countries. Both wP and aP are usually administered in combination with diphtheria and tetanus toxoids(DTwP or DTaP).

Chapter Six: Vaccine available in Bangladesh

Vaccine available in Bangladesh market

Disease	Vaccine	Company name
Hepatitis A	Avaxim Inj.	Sanofi-Aventis
Hepatitis B	Engerix-B	GSK
Pneumonia	Pneumo Inj.	Sanofi-Aventis
Rabies	Rabipur	Renata
Polio	Imovax polio Inj.	Sanofi-Aventis
Human papilloma	Cervarix Inj.	GSK
Meningococcal Disease	Meningococcal(A+C)Inj	Sanofi-Aventis
MMR	Priorix Inj.	GSK
Influenza	Agrippal S1 Inj.	Novartis
Tetanus	TT VAX Inj.	Popular
Typhoid Fever		Incepta
Chicken pox	Varilrix Inj.	GSK
Hemophilus Influenza Type B	Pentaxim Inj.	Sanofi-Aventis
Cholera	Dukoral oral Vaccine	Healthcare

Chapter Seven: Conclusion

Conclusion: These few episodes in the past illustrate the close relationship between veterinary and human vaccines that still holds true today, and a whole book could be written on the subject. Nowadays, as in the past, when there are both human and animal forms of a disease, sometimes it is the human vaccine that arrives first and sometimes the animal vaccine. Whichever comes first serves as a guide for the other. An area where advances in veterinary vaccines are particularly well developed is in parasitic diseases. For instance, although a human vaccine against human schistosomiasis is still not available, there is a satisfactory vaccine against bovine schistosomiasis, even though the parasite involved is very similar to *Schistosoma mansoni*. There is also a vaccine against bovine lungworm, based on irradiated larvae. We are still awaiting one or more of the promised vaccines against malaria, whereas a vaccine against canine babesiosis is already on the market. Where there is a risk of epizootic diseases passing to humans as a result of a reassortment involving different strains, as in the case of avian influenza, physicians see the animal vaccine as the first line of defence in avoiding a possible pandemic. The very latest human vaccine against rotaviruses, the result of a cross between an avian strain and an attenuated bovine strain, is a reminder of what the history of vaccination has revealed: the movement of pathogens between species can pose a very real threat but can also be exploited for prophylactic purposes. Another line of convergence between human and veterinary vaccines has arisen in recent years. In the legislation to ensure greater reliability and safety of vaccines, we see the extent to which veterinary vaccines are now controlled at all stages of trials before being licensed, in a way that does not fundamentally differ from the situation with human medicine. This tendency to converge merely confirms the historic vocation of these ‘two medicines’ to work together. Nowhere is this more apparent than in the history of vaccinology, to which so many veterinarians have contributed.

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