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VIRAL VACCINES AND ANTIVIRALS: Current Use and Future Prospects[1]

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Introduction

Although a variety of approaches have been used in an effort to control viral diseases, e.g. improved sanitation measures, vector control and quarantine, significant advances in disease prevention have occurred largely through the development and application of live or inactivated vaccines (37–39, 47, 48, 57, 64, 65). While in recent years considerable progress has been made in the isolation and characterization of natural materials and synthetic compounds for use as antiviral agents (28–30, 54, 60, 67), perhaps a dozen or so drugs are now available that show promise, and only a few of these have been approved for commerical marketing as antivirals. Recent developments in biotechnology have afforded several basic techniques now being utilized in virus characterization and in the production of specific viral antigens that can be applied to the production of subunit vaccines. Indeed, advances in molecular genetics (gene sequencing), the development of DNA recombinant products, and the production and application of monoclonal antibodies coupled with a "quantum leap" in our understanding of the immune system presage a new era of vaccine development.

In this chapter we present an overview of (*a*) the current status of licensed vaccines; (*b*) the prospects for new or improved immunizing antigens employing the new technologies; and (*c*) the outlook for specific antiviral materials, including interferon and synthetic drugs.[2]

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[2]Acquired immune deficiency syndrome (AIDS) is discussed in a separate chapter in this volume (see 50a).

Information concerning viral vaccines that are licensed in the US and are available for use is presented in Table 1.

Poliovirus Vaccines

The introduction of inactivated poliovirus vaccine (IPV) in 1955 and live oral poliovirus vaccine (OPV) in the early 1960s heralded a sharp reduction in the incidence of poliomyelitis in all parts of the industrialized world. The rapid, dramatic control of this disease is considered to be one of the major achievements of the century. Before the introduction of vaccines there were approximately 200,000 cases of poliomyelitis occurring each year in the United States; now there are less than ten (49). Despite this great success, controversy still abounds as to the relative merits of IPV and OPV, based in part on concerns regarding OPV vaccine-associated paralysis. It is estimated that this risk is approximately one instance of paralysis per three million vaccinations. In the period 1973–1984, 138 cases of paralytic poliomyelitis were reported in the United States. Of these, 85 (62%) were epidemiologically associated with receipt of OPV or contact with a recent vaccine recipient. Thirty-five (41%) of these cases were in recipients and the remaining 50 cases occurred in known contacts of OPV recipients (11).

Table 1 Viral vaccines currently licensed and distributed in the United States

Vaccine	Type of vaccine	
	Live	Inactivated
Poliomyelitis (Types 1, 2, 3)	Primary cercopithecus kidney	Primary cercopithecus kidney
Measles[a]	Primary chick embryo fibroblasts	
Mumps[a]	Primary chick embryo fibroblasts	
Rubella[a]	Human diploid fibroblasts (WI-38)	
Influenza (Type A and B)		Embryonated hen's egg (allantoic fluid)
Rabies		Human diploid fibroblasts (MRC-5)
Hepatitis B		HB_s Ag positive human plasma
		Recombinant yeast
Yellow fever	Embryonated hen's egg (embryo tissue)	
Adenovirus[b] (Types 4 and 7)	Human diploid fibroblasts (WI-38)	

[a]Available in combined forms: measles/rubella, measles/mumps/rubella, and rubella/mumps.
[b]Recommended for use in military populations only.

Use patterns in various countries have ranged from the exclusive use of OPV to complete reliance on the inactivated product. Both IPV and OPV are licensed and available in the US and both products are considered effective in preventing poliomyelitis. Before 1962 and the introduction of OPV, approximately 28,000,000 doses of IPV were administered. Since 1963 when trivalent OPV became available, this product has been used almost exclusively in the nation's immunization programs. The selection of OPV as the vaccine of choice was recommended by both the Public Health Service Advisory Committee on Immunization Practices and the Committee on Infectious Diseases of the American Academy of Pediatrics, as well as an expert committee of the Institute of Medicine, National Academy of Science (50, 55). It is believed that when the benefits and risks for the whole population are considered, OPV is preferable to IPV because it induces intestinal immunity, is simple to administer, is well accepted by patients, and has a record of having essentially eliminated disease associated with wild polioviruses in this country. The unqualified success achieved is largely a result of intensive efforts in immunizing children and continued ability to maintain high vaccination rates (32).

For unvaccinated adults at increased risk of exposure to poliomyelitis, primary immunization with IPV is recommended because the risk of vaccine-associated paralysis is slightly higher in adults than children (6). A resurgence of interest in IPV has occurred in the last several years with the development in Holland and France of an improved IPV vaccine with much higher potency (63). In trials conducted in Europe and Africa it was concluded that a trivalent vaccine containing approximately 40, 8, and 32 D-antigen units, respectively, would provide satisfactory immunity after administration of two doses. In studies carried out in Senegal, six months after the second dose of diphtheria tetanus toxoids pertussis vaccine (DTP) and poliovirus vaccine, 97.4%, 97.7%, and 90% of subjects (two to eight months old at the start) had detectable antibody to poliovirus types 1, 2, and 3, respectively (59). In the control group (individuals who had received DTP but not poliovirus vaccine) 50%, 38% and 80% had antibody to poliovirus, types 1, 2, and 3, respectively, acquired by natural infection during the year of the study.

Trials are now under way in the United States to compare the new IPV product with OPV. Preliminary results comparing OPV and an IPV that was prepared by new improved production procedures in cercopithecus kidney (VERO) cells have been reported by McBean et al (45). As might be expected, only 12 of the 439 two-month-old children entered into the study did not already have maternally acquired antibodies to each of the three virus types. Vaccines were administered at 2, 4, and 18 months of age. At 20 months of age, all children but one had detectable antibodies to all three poliovirus types. Significantly higher geometric mean titers against types 1

and 3 were noted in the IPV group (Type 1, 11.36 vs 4.74; Type 3, 18.75 vs 4.38).

Current research on the characterization of polioviruses has centered around the determination of the complete nucleotide sequence in poliovirus RNA. The virus genome encodes a single long polyprotein precursor from which all viral proteins are derived by proteolytic cleavage. Knowledge of the genome sequences and of the proteins involved in cleavage could contribute ultimately to the development of improved live virus vaccines that are attenuated and stable. Further, it has been shown (3, 16) that the viral capsid protein (VP1) of poliovirus induces neutralizing antibodies, thereby suggesting that it may be possible to produce vaccines from such highly purified proteins either by expression of a cloned VP1 gene in bacteria or by chemical synthesis. Whether such vaccines will be of practical value will depend on how effective they are in comparison to existing OPV and IPV vaccines (the antibody levels induced with these experimental preparations are low) as well as how much it will cost to produce them in quantity.

Measles Virus Vaccine

Prior to the introduction of measles vaccines in 1963, infection with measles virus was considered almost inevitable, and an average of 500,000 cases annually was reported in the United States during the years 1950–1962 (41). Measles is considered a serious disease, perhaps the most severe of the childhood exanthems. In earlier centuries mortality was common, and even in recent times, where poor health and nutritional standards have existed, high mortality rates and severe complications are documented (41). In industralized areas, current measles fatality rates are approximately one death per 3000 cases (5). The complications of measles include middle ear and respiratory tract infections. Encephalitis occurs in approximately one of 2000 cases, often followed by permanent brain damage and mental retardation.

In 1963 two measles vaccines were licensed for use in the United States: live attenuated measles virus vaccine, Edmonston type B, and inactivated formalin-treated alum precipitated virus vaccine; neither of these products was problem-free. Since some febrile reactions occurred after injection with the live virus vaccine, many physicians chose simultaneous administration of the vaccine and immune globulin or a regimen combining live and killed vaccines. In 1967 use of the inactivated vaccine was terminated. It was clear that the protective effect of the vaccine was transient. Moreover, some children who had received it developed an unusual response (atypical measles) when exposed to the natural virus or to the live attenuated vaccine (27). The clinical manifestations of atypical measles were suggestive of delayed hypersensitivity and included atypical rash, killed vaccine fever, and in severe instances, pneumonitis and edema of the extremities.

Additional manipulation of the Edmonston type B strain yielded further

attenuated virus strains that permitted the production of effective, less reactive vaccines, and this type of product has been used exclusively in the United States since 1967. The currently used measles vaccine produced in the United States is designated Moraten and was derived from the Edmonston B strain. Live measles vaccine is highly effective in protecting against measles; antibody response to evoked in 95–100% of susceptible recipients. Although the antibody levels seen in vaccine recipients are lower than those occurring as a result of natural measles virus infection, there is no evidence that lower antibody levels are not fully protective. Persistence of antibody and immunity have been documented over a 16-year period (5).

Reactions produced by the attenuated vaccine (fever and rash) occur in 5–15% of vaccine recipients and are generally mild. The frequency of encephalitis occurring temporally with vaccine use is no greater than that reported for unvaccinated populations, nor is there any evidence that the vaccine is associated with increased incidence of subacute sclerosing panencephalitis (SSPE). Indeed, epidemiologic studies indicated a reduction in reported cases of SSPE at a time when a vaccine effect would be expected (34).

The possibility of eradicating measles from the United States was first considered in 1977, and efforts to eliminate the disease are still in progress. Unfortunately, past control measures that involved mostly mass immunization of pre-school and young school-aged children were insufficient. Other strategies such as school immunization laws and exclusion from school of unimmunized children have been implemented in efforts to increase the immunized population. During recent years, with the success of such programs, a higher percentage of cases have occurred in adolescents and young adults, with a rise in the median age of reported cases (10).

Efforts have been made to reimmunize those individuals who received vaccine before their first birthday, killed measles vaccine, killed measles vaccine followed within three months by live measles vaccine, or a measles vaccine of unknown type in the period 1963–1967 (5). The age at which vaccine is administered has since been raised to 15 months in order to avoid the blocking effect of persistent transplacentally acquired antibody. However, infants as young as six months of age may be vaccinated if there is a likely risk of exposure to natural measles virus; these children would then be revaccinated at 15 months of age. A major problem of eradication concerns identification of vaccine "failures" as well as other susceptible populations, particularly preschool children and "pockets" of children who are difficult to reach in immunization programs. Until this is achieved, complete eradication is not possible.

Overall, in 1986 6273 cases of measles were reported, an increase of 110% over the 2822 cases reported during the same period in 1985 (10). Interestingly, the highest incidence rate occurred in children 0–4 years of age,

whereas in 1985 the highest incidence rate was reported for persons in the 15–19-year-old group. The increase reported for preschool children stemmed from two large outbreaks among mostly unvaccinated children.

Mumps Virus Vaccine

In 1967, the year of mumps vaccine licensure, there were 185,691 cases of mumps reported in the United States; in 1986, 5845 cases were reported (15). It is of interest that during the first six months of 1987 more than 9000 mumps cases were reported (15a) largely in middle and high school students. Since an aggressive mumps immunization program was not instituted until 1980, many individuals in this age group never received mumps vaccine. Several groups are now recommending that students born after 1956 be required to present documentation of mumps immunization before matriculation. Mumps occurs primarily in children; only 15% of all reported cases occur in adolescents or adults. The disease is generally not severe; parotitis may be minimal or absent, and it is estimated that 30% of all mumps infections are subclinical. More severe manifestations of the disease may include meningitis and transient deafness; permanent CNS damage or deafness are extremely rare. When mumps occurs in postpubertal populations, oophoritis develops in 5% of infected females and orchitis in 20% of infected males; sterility in males is a rare sequela (23).

Efforts to develop a vaccine against mumps were at first unsuccessful. While the virus was readily propagated in the chick embryo, resultant preparations either caused mumps in recipients or were too over-attenuated to induce antibody (21). Although an inactivated vaccine prepared from concentrated allantoic fluid was developed and available after 1950, it was only minimally effective and saw little use. Subsequently, a live virus vaccine produced in chick embryo cell cultures using an attenuated virus strain (Jeryl Lynn) was found to be safe and effective. The vaccine produces a noncommunicable infection with few side effects. Antibody levels induced by the vaccine are lower than those seen with natural mumps, but clinical trials have indicated the protective efficacy of the product to range from 75–90% (36). Persisting antibody levels and continued protection against mumps infection have been observed over a 15-year period. Since licensure, more than 60 million doses have been distributed. By 1984 the incidence of mumps had dropped to 1.3 cases per 100,000 population, a 98% decrease from the total cases in 1968, one year after licensure of the vaccine.

Mumps vaccine is available as a monovalent preparation, or in combination as rubella-mumps or as measles-mumps-rubella (MMR) vaccines. The cost-benefit ratio for mumps immunization is greater when mumps vaccine is administered as MMR, and it is recommended that MMR be used in all situations if recipients are likely to be susceptible to measles and rubella as well as mumps.

Rubella Virus Vaccine

Rubella as a common childhood infection is usually mild, of short duration (approximately three days), and accompanied by low-grade fever, lymphadenopathy, and a maculopapular rash. Because of the mildness and variability of symptoms, the disease can go unrecognized. Rubella is much less communicable than measles, and prior to the introduction of vaccines it is estimated that between 10 and 40% of the population could reach adulthood without experiencing rubella infection (22, 69). Thus, many women of the child-bearing age were rubella-susceptible.

The devastating effects of congenital infection were first described in 1941, and the events occurring during the rubella pandemic of 1964–1965 underscored the need for aggressive programs to control rubella. During this latter period an estimated 20,000 congenitally infected infants were born and 11,000 miscarriages, abortions, and stillbirths recorded (66). The risk of severe congenital effects is highest in fetuses infected in the early weeks of gestation. The syndrome can involve the eye, inner ear, heart, and brain. Other resulting defects include hepatitis, low birth weight, bone lesions, and poor growth and development. If the infection is serious, spontaneous abortion and stillbirth may occur.

The first rubella immunization strategy developed in late 1969 in the United States called for large-scale campaigns to immunize all children on or after their first birthday. By 1976, the success of the program was clearly evident; acquired rubella dropped from the 1969 level of 51,686 reported cases to 12,400. However, rubella outbreaks were reported among older individuals in schools, colleges, and hospitals, and in 1977 the number of cases of acquired rubella rose to 20,300 (1).

The advent of the National Childhood Immunization Program in 1977 and the Measles Elimination Program of 1978 both contributed significantly to the effective control of rubella. In addition, increased efforts were undertaken to immunize women of child-bearing age. Since 1977 a downward trend in reported cases of rubella has been observed by the Centers for Disease Control (1). In 1986 there were 500 cases of rubella reported in the United States, representing the lowest number of cases reported since 1966, when the disease first became notifiable (15).

Unfortunately, outbreaks of rubella continue to occur. In 1985 there were three outbreaks in New York City involving 113 individuals. By mid-December of 1986, nine cases of congenital rubella were reported in that city; eight of these were related to the 1985 outbreak (14). Since approximately 8 to 10% of post-pubertal women show no serologic evidence of immunity to rubella virus, the risk of congenital rubella and its serious consequences still remains.

Further decline in the incidence of rubella and congenital rubella syndrome could occur with increased immunization activities, e.g. requiring proof of

immunity prior to college entry, vaccination of susceptible women identified by premarital serology, and vaccination of women after childbirth, miscarriage, or abortion. Rubella vaccine should not be given to pregnant women for any reason, although data collected since 1971 indicate that vaccination within the first three months of conception poses little risk of congenital rubella syndrome and should not be a reason for interruption of pregnancy. However, the pregnant women and her physician should make the decision (7a).

Influenza Virus Vaccine

Influenza, sometimes termed "the last of the great plagues," still represents a major challenge in terms of effective immunization and control. The chief reason for this, particularly among the Type A viruses, is the continued antigenic variation of the viral surface glycoproteins, both of the hemagglutinin (H) and neuraminidase (N) moieties. Minor amino acid changes at antigenic sites are termed "antigenic drift," while major changes in H or N structure that result in new viral subtypes represent "antigenic shifts." Immunity to influenza virus depends on prior experience with the H and N antigens and the development of specific antibodies. The occurrence of "drifts" or "shifts" results in the loss of antibody protection; epidemics of influenza are usually associated with gradual antigenic change (drift) and pandemics with abrupt change (shift). Although global surveillance systems exist wherein new influenza variants are promptly identified, it is not possible to predict the type of change or when it will occur.

When an epidemic or pandemic occurs, influenza virus results in high attack rates of acute illness, with the frequent occurrence of lower respiratory tract complications. Also, influenza often strikes individuals who because of age or underlying health status are unable to cope with the disease and require medical care including hospitalization. Individuals in this situation are considered at "high risk." In a single study, noted by the CDC (12), rates of hospitalization for high-risk adults increased during major epidemics by approximately two- to five-fold in different age groups, reaching a maximum rate of about 800 per 100,000 high-risk persons. High-risk groups, then, constitute the major target population for receipt of influenza vaccines.

Influenza epidemics cause excess mortality, both from influenza pneumonia and cardiopulmonary disease. In the years 1957–1985, epidemics in the US have been associated 18 times with 10,000 or more excess deaths (12). During the 1985–1986 influenza season, excess mortality was again observed, with approximately 80–90% of deaths occurring in persons 65 years or older.

The use of influenza vaccines in the United States has been recommended since 1963 (19). Vaccines currently used are prepared from virus grown in

chick embryos. Harvested allantoic fluid is partially purified, inactivated with formalin, and adjusted in antigenic concentration to a dosage that will induce appropriate antibody response in recipients. Such vaccines when given in the late summer or fall before the influenza season starts are capable of protecting most recipients against influenza viruses that are the same or antigenically similar to those in the vaccine. Protection against illness has varied from 50 to 90% in civilian populations and 70 to 90% in military populations (12).

Adverse reactions to the vaccine usually occur within 24 hours after administration and include fever, malaise, myalgia, and soreness at the site of inoculation. However, in recent years fewer than one third of vaccinees have been reported to develop systemic symptoms or local redness and induration for one or two days at the site of injection (44). Observed reductions in reaction rates are related to (*a*) increased purity of the vaccines; (*b*) the ability to standardize the products more accurately in terms of quantitative dose; and (*c*) the use of vaccines containing disrupted ("split") viral products as opposed to the more reactive whole virion. Since 1976, when vaccines containing swine influenza antigens were used, there has been no evidence that the use of influenza vaccines is associated with an increased frequency of Guillain-Barré syndrome (42).

Influenza vaccine is currently recommended for high-risk persons six months of age or older as well as residents of nursing homes and other chronic care facilities. Groups at moderate risk for whom the vaccine is also recommended include healthy individuals 65 years or older, adults and children with chronic diseases, children receiving long-term aspirin therapy, personnel in contact with high-risk patients, and providers of care to high-risk persons in the home setting (visiting nurses, etc) (12).

The synthetic drug, amantadine hydrochloride, has been shown to be effective against strains of type A influenza viruses but not type B. Amantadine prophylaxis can effectively control influenza A outbreaks if given to all residents in an affected institution. Amantadine is also recommended as an adjunct to late immunization of high risk individuals, for individuals in a household setting caring for family members with the disease, for immunodeficient individuals, and for those for whom influenza vaccine is contraindicated because of hypersensitivity (12, 18).

Rabies Vaccine

The occurrence of rabies in humans in the United States is rare and has decreased from an average of 22 cases per year in 1946–1950 to 0–5 cases per year since 1960 (7). Similarly, the number of cases of rabies in domestic animals (dogs and cats) has decreased steadily from 8000 reported cases in 1946 to 220 in 1984 (13). However, bites by dogs and cats continue as major reasons given for receiving antirabies treatment. Sylvan rabies continues to

serve as a reservoir of infection. Reported cases of rabies in wild animals (foxes, skunks, raccoons, and bats) have increased over the past decade, with approximately 3300 cases reported in 1984 (13).

Each year in the United States approximately 25,000 individuals receive postexposure rabies prophylaxis consisting of vaccines inducing an active immune response and simultaneously administered globulins that can provide rapid passive immune protection. The current rabies vaccine represents the evolutionary product of one of the first vaccines to be developed. The original rabies vaccine, Pasteur's partially inactivated fixed virus prepared from infected rabbit central nervous system (CNS) tissue, was followed by Semple's fully inactivated formalin-treated virus, then by a vaccine propagated in duck embryo and devoid of CNS tissue, and, finally, by a vaccine made in human diploid cells and inactivated with β-propriolactone and/or tri-*N*-butylphosphate grown (68). This latest vaccine, when used with rabies immune globulin (RIG) or anti-rabies serum (ARS), has been shown to be protective in nearly 600 individuals bitten by rapid animals in several areas of the world (Iran, Germany, and the United States). The use of RIG over ARS is recommended, since the latter product, prepared from hyperimmunized horses, has a much higher risk of adverse reactions (7).

Since the new vaccine causes many fewer adverse reactions than the earlier products, a regimen of preexposure immunization is also recommended. Those at high risk include laboratory workers, veterinarians, wild life workers, and travelers to areas where rabies is epizootic. Individuals in high risk groups are given three 1.0 ml injections (days 0, 7, and 28). If there is evidence of exposure, then two additional doses of vaccine are administered, one as close to the time of exposure as possible and the other three days later. RIG is not recommended for those who have received preexposure immunization. Thus, while preexposure immunization does not obviate the need for postexposure prophylaxis, it may protect those whose exposure to rabies is inapparent or those whose postexposure treatment might be delayed, and, finally, it reduces the number of postexposure vaccine doses required and eliminates the need for RIG.

Hepatitis B Vaccine

Hepatitis B virus (HBV) is a pathogen of public health importance in nearly all parts of the world. Infection is often persistent, particularly in children infected perinatally or early in life; worldwide there are approximately 200 million carriers (64). Infection with HBV may lead to chronic persistent hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. In the United States it is estimated, based on overall incidence (11.1/100,000 in 1985), that more than 300,000 HBV infections occur annually (9).

Although the discovery of Australia antigen (HBV surface antigen—

HBsAg) in 1965 provided the means for successful development and application of screening procedures to rule out antigen-positive blood donors and to interdict contaminated blood and plasma destined for use in transfusions or product manufacture, conventional efforts to propagate HBV in cell culture were uniformly negative. Based on the observations of Krugman et al (43) that boiled HBsAg-containing serum lost infectivity but not immunogenicity, effective experimental subunit vaccines were prepared from human plasma obtained from chronic HBsAg carriers. A licensed vaccine first became available in 1982. The product is a purified suspension of 22 nm alum-adsorbed HBsAg particles, inactivated using three separate procedures, viz. treatment with 8M urea, pepsin at pH2, and formalin, 1:4000. These inactivation steps also serve to render harmless other potential virus contaminants of blood, including human immune deficiency virus (HIV).

Clinical trials with the plasma vaccine were conducted between November 1975 and June 1982 in approximately 19,500 volunteers (46). Target populations included male homosexuals, hemodialysis patients and staff members, health care personnel, infants born to carrier mothers, and low-risk adult males. Administration of vaccine did not cause any serious adverse reactions; the majority of complaints concerned discomfort at the site of injection, headache, fatigue, and upper respiratory or gastrointestinal illness.

Antibodies to HBsAg were induced in more than 90% of healthy adults following a three-dose regimen; a similar response was observed in low-risk healthy children (3 to 12 months of age) who received two doses of vaccine. Protective efficacy of the vaccine was clearly demonstrated in several multicenter studies involving homosexual males; efficacy in the prevention of viremic HBV infection is 85 to 95% and protection is virtually complete for up to two years in those who respond to the vaccine. Studies in infants born to carrier mothers were also encouraging. When both vaccine (three 20 μg doses) and hepatitis B immune globulin (HBIG) were used together, the protective efficacy level was greater than 90%. In hemodialysis patients, however, no efficacy was demonstrated in early studies, perhaps because of low antibody response and a low attack rate of HBV. In a more recent study, antibody was induced in 88% of patients, with an efficacy rate of 78% (51).

A second vaccine, recombinant yeast human hepatitis B vaccine, was licensed in 1986 (40). This vaccine was prepared by inserting the gene region that encodes HBsAg into the yeast, *Saccharomyces cerevisiae*. The HBsAg produced is cell associated and released from the cells by homogenization. The HBsAg particles produced in yeast cells are morphologically similar to those isolated from human plasma.

Immunogenicity studies with the recombinant vaccine indicate that it is comparable to the plasma-derived product (70). Antibodies were induced in 91% of normal adult recipients receiving 10 μg of vaccine in a three-dose

series at 0, 1, and 6 months. In children less than 12 years of age, 99% developed protective levels of antibody in response to three 5 μg doses. Similarly, in 334 adults given a three-dose series of 5 or 10 μg, Davidson & Krugman (20) observed seroconversion rates comparable to those seen in adults receiving 20 μg of the plasma vaccine. Low antibody responses were observed when only 2.5 μg doses were given; however, strong booster responses were obtained after a fourth dose given at 12 months. Vaccine efficacy has been demonstrated in chimpanzees and in a small number of infants born to HBsAg-positive mothers; additional efficacy studies are under way.

Yellow Fever Vaccine

Yellow fever currently occurs in Africa and South America and exists in two indistinguishable forms, urban and sylvan or jungle. Urban yellow fever is found in humans and is transmitted by the mosquito, *Aedes egypti,* whereas jungle yellow fever occurs as an enzootic disease of nonhuman primates and is transmitted by several *Aedes* species. Eradication of *A. aegypti* and immunization are the best means for preventing urban yellow fever, while jungle yellow fever is controlled in humans by immunization. WHO is considering a recommendation that yellow fever vaccine be used routinely in childhood immunization in those persons living in endemic areas (4).

A successful live, attenuated vaccine against yellow fever was first developed in the early 1930s but only after many years of effort to attenuate the virus in either mice or chick embryos (62). Early products were either over- or under-attenuated, and it was recognized that candidate strains must be carefully manipulated to avoid changes in characteristics of the virus that might render it unsafe for human use. With the selection of the 17D strain for vaccine production in the United States came the introduction of the seed lot system and ancillary procedures for assuring consistency of the vaccine virus. A major problem with the vaccine occurred in the early 1960s when Rubin (56) demonstrated that chicken flocks were almost universally infected with viruses of the avian leukosis complex (ALV). Clearly, all chick-embryo-produced vaccine as well as the 17D seed material were contaminated. Based on the severity of yellow fever and on concerns of altering the seed virus while attempting to free it of ALV, the decision was made to continue use of the available vaccine despite ALV contamination. The issue was ultimately resolved with the development of ALV-free chicken flocks and the successful preparation of a ALV-free 17D seed virus. Today's vaccine is regarded as highly safe and effective; a single subcutaneous dose confers immunity that persists for more than ten years (8, 52). The vaccine is currently recommended for persons six months of age or older traveling or living in areas in which yellow fever exists as well as for laboratory personnel exposed to virulent yellow fever virus (8).

Future Prospects

The basic techniques of recombinant DNA production of polypeptides and proteins and the hybridoma production of monoclonal antibodies have enhanced the quality and number of technical alternatives available in attempting to improve and expand our armamentarium of viral vaccines (24, 25, 53). The new types of experimental products include the following:

1. *Synthetic peptides:* laboratory-produced peptides that contain the critical protective immunogenic segment of viral surface antigen.
2. *Subunit vaccines:* specific viral proteins isolated through gene cloning and produced in microbial or mammalian cells.
3. *Vector vaccines:* live virus product created by inserting the essential antigenic determinants of a particular viral pathogen into a vector virus, e.g. vaccinia.
4. *Reassortant vaccines:* hybrid virus product in which the new virus is nonpathogenic but contains those genes of the pathogen which code for its protective surface antigen.
5. *Anti-iodiotypic antibody vaccines:* based on formation of anti-antibodies; prepared by producing monoclonal antibody specific for a pathogen's protective antigen; the resultant antibody is then injected into an animal, thus inducing the formation of an anti-antibody or anti-idiotype. When the anti-idiotype is injected into the recipient it induces antibody that cross-reacts with the original viral antigen; thus, the anti-idiotype can be used as a vaccine.

Table 2 lists some of the viral vaccines now under development and the kinds of technology being applied (53). It should be remembered that although our ability to manipulate viruses in the laboratory can significantly shorten the time required to develop a new product, that product must undergo extensive laboratory and clinical testing before it can be licensed and distributed to the public. However, the methods now exist that can broaden the scope of vaccine use and result in major achievements in control of human disease.

Antiviral Substances

SYNTHETIC DRUGS With the discovery and rapid development of antibacterial compounds during the early 1950s came the hope that similar progress would be made in finding specific "miracle drugs" for the treatment of viral diseases. An interesting history of the discovery and application of antiviral drugs was published in 1985 (2). Until the recent rapid expansion of technologies available for virus manipulation, the development of effective antivirals had been a slow, painstaking process usually involving large scale random testing and serendipity. It was generally believed that the complex

Table 2 Viral vaccines under development

Vaccine	Elements of experimental production technology
Influenza A & B	Reassortant vaccines; cold adapted mutants or avian influenza strains serve as gene donors
	Subunit hemagglutinin or neuraminidase
Respiratory syncytial virus	Vector vaccine, glycoprotein gene
Parainfluenza	Subunit, trivalent
Hepatitis A	Inactivated, cell cultures
	Attenuated, live
	Subunit
Hepatitis B	Vector vaccine—HBsAg
	Subunit
Herpes simplex	Subunit—glycoprotein
viruses 1 and 2	rDNA—glycoprotein
	Attenuated live
Varicella-Zoster	Attenuated, live
Cytomegalovirus	Attenuated, live
Rotavirus	Attenuated live, bovine
	Attenuated live, simian
	Reassortant (human/simian)
Rabies	rDNA glycoprotein
	Vector vaccine—glycoprotein gene
Yellow fever	Attentuated live, cell cultures
Dengue	Attenuated live, cell cultures
Japanese encephalitis	Inactivated, cell cultures

nature of virus-host cell interaction precluded the development of a broad spectrum antiviral and that the development of a drug specific for a given virus was not technically feasible. Also, prophylactic use of drugs was not practical because of inherent drug toxicity, and by the time that many viral infections could be diagnosed, it would usually be too late to administer the drug. Economic factors have also dampened researchers' enthusiasm, since even the most promising compounds require years of laboratory and clinical testing measured in millions of dollars. Despite these obstacles, several useful drugs have emerged and are approved for use (Table 3).

The successful application of acyclovir against herpes infections and the discovery of Zidovudine (azidothymidine) for use in the treatment of acquired immunodeficiency syndrome (AIDS) have given strong impetus to the search for new antivirals (31). The concept of a targeted approach is now a practical one, since information concerning the structure of viruses and spatial configuration of their proteins is readily available. Such data may be useful in identifying specific target sites for antiviral agents (10).

INTERFERON The discovery of interferon by Isaacs & Lindenmann in 1957 opened up a unique area in the search for antivirals (26). Although a great deal

Table 3 Approved antiviral drugs in current use

Dose	Clinical use	Method of administration
Amantadine	Prophylaxis and treatment of influenza A	Systemic
Trifluorothymidine	Herpes keratitis	Topical
Vidarabine (Adenine arabinoside)	Herpes encephalitis Herpes zoster	Systemic
Acyclovir	Genital herpes	Systemic
Zidovudine (Azidothymidine)	AIDS	Systemic
Ribavirin	Respiratory syncytial virus infection in severely ill infants	Aerosol

has been learned about interferon, the rewards thus far have been disappointing: No interferon product has yet been approved for the prevention or treatment of viral infections and only one use has been approved for the treatment of malignant disease, i.e. interferon alpha for hairy cell leukemia. Interferon was first defined as a substance produced by virus-infected cells which when added to normal cells protected them from viral infection. Subsequent research revealed that other agents, including bacteria, rickettsiae, and synthetic polypeptides, were capable of inducing interferon (61).

For many years it was not possible to obtain high yields of interferon and the majority of studies were carried out using material prepared in human leukocytes. Later, procedures were developed for producing interferon in human diploid fibroblast cells or in human lymphoblastoid cells transformed by Epstein-Barr virus (17, 35). With the successful application of DNA recombinant technology the problems of interferon supply were quickly overcome.

There are three major types of interferon: alpha (leukocyte), beta (fibroblast), and gamma (immune), with several associated subtypes. Whether any one of these types or subtypes is more effective than another remains to be determined. Interferons display a wide range of biological activities in addition to viral inhibition: They can stimulate or depress antibody production, stimulate phagocytosis, enhance the action of natural killer and T-lymphocytes, and inhibit the development of delayed type hypersensitivity (58). In addition, interferons at high dose levels can also be toxic to recipients, making their use a complex issue.

While interferons have been used experimentally in a variety of clinical studies, the most promising area for use appears to be in the treatment of warts. Also, several anecdotal reports describe its efficacy in the treatment of juvenile laryngeal papilloma (33). Additional efficacy studies are in progress.

Summary

The evolution of viral vaccines from the time of Jennerian prophylaxis to today's recombinant technology has been a continuing story of success. From the relatively crude or "first generation" vaccines for smallpox, rabies, and yellow fever followed a second and third generation of improved or new viral vaccines. The application of techniques for attenuating, inactivating, and partially purifying candidate viruses yielded safe, effective vaccines against influenza, poliomyelitis, measles, mumps, and rubella. With the advent of effective national immunization programs in the United States and other areas of the world to promote wide scale use of these vaccines, we have seen a dramatic decrease in incidence of the viral infections of childhood. The new biotechnology serves as the cornerstone for a fourth generation of vaccines and has already provided a licensed recombinant yeast human hepatitis B vaccine. The prospects for a wide spectrum of new or improved vaccines are highly encouraging, not only because of the recent technical advances but also because vaccine development has been recognized as a priority area of research. Under the National Institute of Allergy and Infectious Diseases' Program for Accelerated Development of New Vaccines, support is being provided for developmental vaccine studies with hepatitis A and B, influenza A and B, rabies, rotavirus, varicella, and respiratory syncytial virus (53). The outlook for antivirals is equally optimistic. The same technologies that have provided greater insight into the genetics and molecular biology of viruses and hence the means to fashion subunit or even synthetic vaccines have yielded data that can be applied to successful development of targeted antiviral compounds.

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