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Review article

The need for new antiviral agents

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Summary

Population density and immune status, vectors and virulence of infection, nutritional status, sanitation, genetic susceptibility and medical management of cases, are important factors influencing the incidence and/or severity of virus infections. Thus, the prevalence and clinical importance of virus infections and the need for antiviral drugs differ from place to place and from time to time. National and World Health Statistics of notifications of disease give some index of the incidence of infections but not all virus infections are notifiable. Such statistics can be misleading also through failures to notify from sloth on the part of the physician or, in the absence of pathognomonic symptoms or signs, from errors in diagnosis.

Any assessment of the need for new antiviral drugs should consider the availability, safety, effectiveness and cost of alternative measures, including prevention of spread of infection by control of vectors, immunization by use of viral vaccines, or treatment with existing antiviral drugs. Early start of treatment of acute virus infections with existing drugs gives the best results and, where the clinical diagnosis is uncertain, accurate rapid virus diagnosis is of paramount importance. Many virus infections are asymptomatic or of trivial importance and without sequelae. However, new or improved antiviral drugs are needed for the prevention and/or treatment of a number of significant conditions caused by viruses which are not at present adequately controlled. These include upper and lower respiratory tract infections, influenza, chronic hepatitis, gastroenteritis, infectious mononucleosis, measles, rabies, haemorrhagic fevers and warts. Furthermore, such drugs might prove of therapeutic value in the prevention or treatment of virus-associated tumours, such as hepatoma, nasopharyngeal carcinoma, Burkitt's lymphoma, Kaposi's sarcoma and possibly carcinoma of the cervix.

antivirals; vaccines; immunoglobulins

The need for antiviral drugs is directly dependent on the clinical importance and prevalence of virus infections, on the availability, safety, effectiveness, acceptability and cost of existing antiviral agents including immunoglobulins and vaccines, and on procedures designed to control vectors of infection. In many virus infections, clinical symptoms appear relatively late, and in some they only appear as viral replication ceases. Antivirals could only be of therapeutic value in those infections where symptoms and pathological changes develop in the presence of viral replication. However, prophylactic treatment of contacts is another potentially important indication for some infections. The clinical importance of a virus infection can be assessed according to rates of mortality, morbidity and the frequency of long-term sequelae. Thus, for example, the fatal outcomes associated with clinical rabies and herpes encephalitis confer on these infections an importance different from those of rhinoviruses. Prevalence of infection is highly variable and dependent on many factors, including population density and immune status, genetic susceptibility, geographical location, sanitation, virus virulence, and medical management of cases, with particular reference to quarantine and other procedures which prevent transmission. Clearly, the prevalence of an infection changes, as new vaccines are developed, and according to the success with which programmes for immunization and the control of vectors are implemented.

Prevalence of infection

The prevalence of infections can be assessed by notifications of infectious diseases. It should be recognised that these notifications are based on clinical diagnoses, which are sometimes erroneous, that there are failures to notify, and that atypical and asymptomatic infections often go unrecognised. For example, the proportion of cases of poliomyelitis with paralysis varies from 0.1% to 20% [36,47], infection with influenza may produce symptoms of a common cold without significant systemic illness, and the ratio of cases of rubella with and without rash is reported to vary between 1 : 1 and 1 : 6 [27]. Nevertheless, in Britain national statistics indicate that measles, infective jaundice, and influenza are targets for control (Table 1). Notification statistics, available from 40 general practices covering a sample population of approximately 200 000 persons, would add the common cold, varicella zoster virus infections, and possibly rubella and mumps (Table 2).

Other virus infections are not notifiable because, although prevalent, they do not cause unique and clear-cut clinical syndromes (e.g. respiratory syncytial virus), are not regarded as of national medical importance (e.g. mumps), or because they are important only in special circumstances, for example in pregnancy or in patients with depressed immune systems who are unable to mount a normal immune response against infection (e.g. cytomegalovirus).

TABLE 1

Corrected notifications of selected diseases (England and Wales)

	1980	1981	1982	1983
Poliomyelitis	3	2	2	4
Measles	139485	52974	94195	103700
Infective jaundice	5132	9834	10602	6314
Influenza and influenzal* pneumonia	514	626	716	796
Rabies	-	1	-	-
Smallpox	-	-	-	-
Yellow fever	-	-	-	-
Lassa fever Viral haemorrhagic fever Marburg disease	-	-	1	-

From OPCS Monitors MB2/83/2, MB2/85/1.
* Deaths.

TABLE 2

New diagnosed episodes of communicable respiratory disease of viral aetiology from 40 general practices (England and Wales)

Quarter ending December 1983	
Chicken pox	246
Herpes zoster	154
Measles	45
Rubella	106
Infective hepatitis	15
Mumps	220
Infective mononucleosis	61
Common cold	4893
Influenza-like illness	1582
Epidemic influenza	248

From OPCS Monitor MB2/85/1.
Population at risk ca. 200000.

Existing antiviral drugs

A small number of antiviral drugs are licensed (see Table 3). Some are highly active and toxic compounds which limits their use to topical application or the treatment of life-threatening conditions, while for others clinical effectiveness is less clear-cut. A new era of antiviral drugs has been heralded by the introduction of acyclovir, a compound which is highly effective against herpes group viruses, notably herpes simplex and varicella zoster viruses, has a mode of action which protects uninfected cells, can be given systemically and is essentially without significant side-effects.

TABLE 3

Antiviral drugs presently licensed in Great Britain

Virus group	Virus type	Drug	Formulation available
Pox	Smallpox	Methisazone	oral*
Herpes	Herpes simplex	Idoxuridine	topical
		Vidarabine	topical
		Acyclovir	topical, parenteral, oral
	Herpes zoster	Idoxuridine	topical
		Vidarabine	parenteral
		Acyclovir	parenteral
Myxovirus	Influenza A	Amantadine	oral

* Obsolete.

Immunoglobulins

Infection-specific immunoglobulins are available against measles, hepatitis B, varicella zoster and rabies viruses. Immunoglobulins provide temporary protection against infectious disease, an important use being for example the protection of travellers against hepatitis. However, results in the treatment of infectious virus disease have been unimpressive.

Vaccines

Any consideration of the need for antiviral agents must take into account the availability of safe and effective viral vaccines. In the United Kingdom for example, there are national programmes for vaccination against poliomyelitis (Types I, II and III), measles and rubella (for girls only). In addition, vaccines are recommended for subjects at special risk from influenza and hepatitis B. Yellow fever and rabies vaccines are available for travellers. Mumps vaccine is licensed but is not recommended since it is not considered that the morbidity and sequelae of mumps infection are significant.

Viral vaccines are either live or inactivated. Measles, rubella, mumps, yellow fever and oral poliomyelitis vaccines are live, vaccinated subjects being inoculated with an attenuated infection, which elicits protective immune responses of long or life-long duration but causes few if any symptoms of natural infection. For all except oral poliomyelitis vaccine a single dose of vaccine constitutes a primary immunization course. Such vaccines are highly effective in developed countries. However, since they may be inactivated at temperatures above 10°C, the maintenance of a cold chain from manufacturer to vaccinee is of paramount importance. This cold chain may be breached in developing countries, particularly those with high ambient temperatures.

In comparison, inactivated virus vaccines (for example influenza, rabies, inactivated poliomyelitis and hepatitis B) usually require several doses in a primary immunization course, and elicit less durable immune responses requiring the administration of reinforcing doses.

Virus infections against which there are national immunisation programmes

Poliomyelitis

Polio virus replication occurs in the intestinal tract and lymph nodes, followed by viraemia, sometimes with nervous system involvement leading to paralysis. Often, when nervous system involvement occurs, the infection is biphasic, with a minor illness in the first phase with viraemia, then a remission of 4–6 days, followed by recurrence of fever and the development of paralysis or meningitis. Immunoglobulins are of little value unless given before viraemia has occurred, but at this stage, cases are not readily identified.

Oral poliomyelitis vaccines are highly effective and poliomyelitis is not at present a threat in developed countries. In Britain the annual uptake of vaccine has been maintained between 70% and 80%, while concern about the safety of the simultaneously administered whooping cough vaccine has reduced the uptake of the latter from 80% to less than 40%. However, oral poliomyelitis vaccine is not totally safe, in that vaccine-associated paralysis occurs in recipients and in contacts of vaccinees at estimated frequencies respectively of 0.2 and 0.4 per million doses of vaccine administered [45]. The use of inactivated poliomyelitis vaccine would obviate vaccine-associated paralysis, but it is possible that an uptake level as low as that currently seen for oral vaccine would be insufficient to prevent outbreaks.

Many countries in Africa, Asia and continental America, excluding the United States and Canada, report means of 5000 cases of paralytic poliomyelitis annually [29]. Paccaud [29] comments that the world may be divided into two groups – countries with nationwide poliomyelitis vaccination campaigns, where the incidence approaches zero, and countries without such programmes, where the incidence is increasing. In the latter, improvements in living standards have been associated with delays in the age at which infection occurs, leading to an increased incidence of paralysis. Furthermore, in tropical countries, live vaccine has frequently been shown to elicit poor seroconversion rates, results which have been attributed to breaches in the cold chain, interfering enterovirus infections and/or inactivation of vaccine virus by antiviral agents present in saliva. However, a mass immunization programme was effective on controlling an outbreak of poliomyelitis within twelve days of its initiation [35]. Thus, the development of anti-poliomyelitis virus drugs seems of secondary importance to the implementation of aggressive poliomyelitis vaccination programmes using either live or killed vaccines.

Measles

With measles, viraemia occurs about the 6th–8th day after infection and the first catarrhal symptoms develop on the 10th–11th day. The rash appears on the 14th day simultaneously with the end of virus replication and the development of antibody. In developed countries measles is rarely life-threatening in immune competent children, but carries a significant morbidity mainly due to bacterial superinfection of the respiratory tract but also to an occasional (0.1%) case of encephalitis. High measles mortality rates are seen in malnourished children in tropical, developing countries and in children who are immune-compromised [19]. In the United States, health authorities aim to eradicate measles by requiring that all children attending school are immune as a result of previous natural infection or vaccination. During 1980 only 13 506 cases of measles were reported in the whole of the United States, in comparison with almost 150 000 in England and Wales [2,28]. In 1982 in the United States, and England and Wales respectively 1697 and 94 193 cases were notified. The measles vaccine uptake in the U.S.A. is over 90%, whereas that in Britain is about 50% [5]. The National Childhood Encephalopathy Study demonstrated that vaccinated children are 2.5 to 3.9 times more likely to develop encephalitis 7–14 days after vaccination than unvaccinated control children [56]. Nevertheless, the estimated 1 : 87 000 risk of encephalitis within 14 days of vaccination is significantly less than that associated with natural infection. It will be some time before western European countries approach the control of measles achieved in the United States. Anti-measles compounds would be of some value for the treatment of children in developing countries, for children with serious measles in developed countries, and for children who are immune-compromised. However, since virus replication ceases when the rash appears, early diagnosis and treatment would be critical. In addition, such compounds might be effective in the management of patients with subacute sclerosing panencephalitis, a rare condition caused by persistent measles infection of the central nervous system which gives rise to progressive neurological dysfunction and death.

Rubella

Rubella is a mild infection without significant sequelae, which would barely be worth prevention or treatment were it not for its teratogenic effects in pregnancy. Following the 1964 outbreak of rubella in the United States, the New York University Medical Center cared for over 300 children with congenital defects following maternal rubella, of which deafness, blindness, heart disease, psychomotor retardation and death were consequences. They estimated that maternal and child care for 100 typical surviving children would cost over $2000 million [4]. Live vaccines which are safe and effective are available and with uptakes of over 90% in young children have reduced the incidence of congenital rubella in the United States [16]. However, so far, rubella vaccination programmes in Europe have shown little effect. The UK National Congenital Rubella Surveillance Programme documented 536 cases of confirmed or suspected congenital rubella during the decade from 1970 to 1979 inclusive [46]. Of these about 25% gave no history of illness, or contact and would not therefore have

presented as candidates for antiviral therapy. However, significant additional numbers of at risk pregnancies are terminated. There is clearly at present a limited but individually important need for anti-rubella virus chemotherapy. Nevertheless, the development of a compound specifically for use in pregnancy would present some difficulties.

Infections for which vaccines are available for those at special risk

Influenza

From 1971 to 1975 inclusive there were in Britain over 38 million days of certified incapacity from influenza in males alone [5]. Influenza poses a greater risk to patients with chronic respiratory illness and other chronic diseases than to the normal population. The control of influenza by vaccination presents special problems because of the ability of infuenza viruses to recombine and to give new antigenic types which evade immunity generated by previous natural infection or by vaccination. Major antigenic changes preceded the worldwide pandemics of 1918, 1957 and 1968, while smaller antigenic changes have been associated with smaller outbreaks. While inactivated influenza vaccines clearly protect against infection with homologous strains, the propensity of wild virus to undergo antigenic changes makes vaccination against influenza a less certain and effective procedure than is the case for other viruses. It is generally recommended that vaccination be restricted to special risk groups [3].

Some drugs with anti-influenza virus activity are available. Amantadine inhibits penetration of influenza virus (A strain) into host cells and has been shown in placebo-controlled trials to prevent infection with sub-types H_1N_1, H_2N_2 and H_3N_2. In therapeutic trials, amantadine has been shown to give more rapid recovery and to curtail the amount and duration of virus shedding [48]. Amantadine is also used in the treatment of Parkinson's disease. It has not received wide acceptance as an antiviral agent, probably because of incomplete effectiveness, the occurrence of minor side effects, and the absence of activity against influenza virus B strains. In the presence of outbreaks of influenza A there is merit in the prophylactic administration of amantadine to high risk patients. In contrast, the advantages of its use in sporadic cases of influenza are less clear. Since illnesses caused by A and B strains are not distinguishable on clinical grounds, and rapid laboratory techniques to identify the causative virus are not routinely done, practitioners do not know whether an individual is infected with an A or B strain, or even with some other agent.

Rimantadine, an analogue of amantadine, has at least equivalent prophylactic and therapeutic activity but causes fewer side effects [6,48,58].

Ribavirin, when administered by aerosol, has been shown to be effective in the prevention of infection with A and B strains, and also in the treatment of experimental infections with respiratory syncytial virus [14]. Despite the availability of amantadine and the development of rimantadine and ribavirin, there remains a need for effective broad spectrum antiviral agents that can be used to prevent and to treat influenza and other viral respiratory infections.

Viral hepatitis

The term 'viral hepatitis' applies to several clinically similar disease entities. Hepatitis A is caused by a picornavirus which occurs commonly, with over 50% of the population having serological evidence of infection by adulthood. The agent is transmitted by the faeco-oral route. Infection is usually acute, with symptoms of fever, malaise, anorexia, mild abdominal discomfort and jaundice, although asymptomatic and anicteric cases occur. The mortality rate is low (< 1%) and chronic infection leading to cirrhosis has not been demonstrated. As yet no vaccines against hepatitis A are licensed but short-term protection against infection may be achieved by administration of immune serum globulin, which is recommended for certain classes of contacts according to the degree of risk. Since clinical symptoms appear as virus shedding ceases, the development of anti-hepatitis A virus agents does not seem to be an important target.

Hepatitis B is caused by a hepadnavirus. It is an insidious infection with symptoms of anorexia, nausea, vomiting, malaise, abdominal pain, jaundice and joint involvement. Infection is transmitted in infected serum or blood inoculated by hypodermic needles, or through abraided skin or mucous membranes. About 10% of patients develop a chronic carrier state, which may be either asymptomatic or associated with active liver disease. Patients with chronic infection may develop cirrhosis of the liver and primary hepato-cellular cancer [9]. In the United States about 15 000 cases of hepatitis B infection are reported annually although it is estimated that only 10–25% of cases are notified [59]. In 1977, there were over 30 000 deaths from hepatic cirrhosis and 2400 deaths due to primary hepato-cellular carcinoma, of which respectively 11% and about 36% were attributed to hepatitis B [9]. The incidence may be lower in the United Kingdom, since in England and Wales only 5132 cases of infective jaundice were notified in 1980. The incidence of hepatitis B is higher in other populations (for example the Chinese) where infection early in life is frequent and followed by a significant incidence of primary hepatocellular carcinoma.

Hepatitis B vaccines have recently become available and are recommended for immunization of classes of subjects at special risk from infection, e.g. drug addicts, haemophiliacs, homosexuals, mentally defectives and medical and paramedical staff who care for them. Short-term protection against hepatitis B may be achieved by the administration of hepatitis B immunoglobulin, or alternatively immune serum globulin and is recommended for contacts. Human hepatitis B virus cannot readily be propagated in tissue culture or animals. Animal models of infection with related hepatitis viruses are being developed. Until now therefore assessments of the antiviral activity of test agents have been carried out directly in human subjects, monitoring virus markers of infection. The antiviral effects of interferon, adenosine arabinoside, adenosine arabinoside monophosphate, acyclovir, and combinations of some of these agents have been studied in patients with chronic infections [40,44,50,52]. All these agents have been shown to affect markers of virus replication in the short-term. However, virus replication usually returns to pre-treatment levels once short-term antiviral therapy has been stopped. There are two important targets for antiviral therapy in this condition: to convert infectious carriers to non-infectious carriers, and

to eradicate infection thereby preventing further liver damage and the long-term sequelae of cirrhosis and cancer.

Rabies

In human subjects, clinically manifest rabies is almost always fatal. No continents are free from rabies, except Australia and Antarctica. In 1976 rabies was reported from 22 of 32 European countries and in the 5 year period from 1972–76 there were over 82 000 laboratory-confirmed cases in animals, and post-exposure treatment was given to over a million people. Despite these precautions, there were over 600 deaths from rabies in Europe during this period [49]. In 1978, 115 cases were documented in Algeria, 158 in Bangladesh, and 178 in Burma [57].

Rabies develops in 35–60% of subjects following a bite by an infected animal. During the incubation period of 3–8 weeks, the virus invades the central nervous system by traveling along nerves from the site of injury and then causes convulsions, coma and death. Post-exposure treatment with rabies vaccines and specific immunoglobulin is effective if given early. Early treatment of experimental infections in monkeys, with human leucocyte interferon administered intramuscularly and into the cerebro-spinal fluid increased survival, in comparison with controls [51]. Some human cases have been treated with interferon but without apparent improvement [25]. Antiviral agents with activity against rabies would therefore be of considerable interest.

Virus infections caused by herpes viruses

Several herpetoviridae occur commonly in humans. All of them (herpes simplex virus, varicella zoster virus, cytomegalovirus and Epstein–Barr virus) have the characteristic of latency after primary infection.

Herpes simplex virus

Herpes simplex virus (HSV) causes a spectrum of diseases, ranging from those with a high mortality rate (encephalitis, disseminated neonatal herpes) to those of moderate morbidity (herpes keratitis, genital herpes) and those of less consequence (herpes labialis ['cold sores']). Classically, HSV Type I virus causes cold sores, most cases of keratitis and encephalopathy, while Type II virus causes genital herpes. With the exception of encephalitis, recurrent episodes of infection are common for all these conditions. Orofacial mucocutaneous herpetic lesions are frequent in immune-compromised patients under treatment with cytotoxic or immune-suppressive drugs for malignant disease, or following cardiac, renal or bone marrow transplantation. If the immune suppression remains unchanged, these may lead to persistent lesions, to dissemination of infection and sometimes to death.

Attempts are being made to develop inactivated sub-unit HSV vaccines but these are not yet licensed. They have been shown to be effective in the prevention of

experimental infections in model systems in animals and, if given before infection in man, might be able to prevent primary and recurrent infection. Since recurrent infections occur in the presence of circulating antibody, vaccines may be ineffective in reducing the frequency of episodes in sufferers. Ophthalmic preparations of idoxuridine, vidarabine, trifluorothymidine and acyclovir have all been shown to be effective in the treatment of herpetic eye disease [7]. Intravenously administered vidarabine has been shown to be effective in the treatment of HSV encephalitis [53] and neonatal herpes [54]. Intravenous acyclovir is effective in the treatment of HSV encephalitis [42] and in the prevention and treatment of HSV infections in immune-compromised patients [41].

Oral and topical acyclovir (cream formulation) has been shown to be effective in the treatment of initial and recurrent genital herpes, and the topical formulation in the treatment of herpes labialis [8,26]. Encouraging results have also been obtained in the suppression of frequent recurrent infection with oral acyclovir [24].

Varicella zoster infections

Primary infection with varicella zoster virus (VZV) is the cause of varicella (chicken pox). The virus remains latent after primary infection until there is a failure in immune surveillance and recurrent lesions present as herpes zoster (shingles). The incidence of shingles increases with age, but at all ages is more common when the immune system is compromised. The rash of shingles is acutely painful. After the lesions have healed, patients often suffer prolonged and painful post-herpetic neuralgia.

A live VZV vaccine has been developed. However, chicken pox is not a serious infection in immune competent children and prevention or treatment is only clearly merited for those who are immune-compromised. There is however a clinical need for the protection of immune-compromised children against chicken pox and a need for antiviral treatment for chicken pox in the immune-compromised, and for shingles in immune-compromised and immune competent subjects. Acyclovir, vidarabine and interferon have all shown beneficial effects in controlled trials [21,30,55]. Several other drugs, including BVDU (bromovinyldeoxyuridine), have interesting activities against VZV.

Cytomegalovirus

In subjects who are otherwise normal, infections with cytomegalovirus (CMV) are almost always asymptomatic. However, infections during pregnancy may infect the fetus, giving rise to fetal damage. It was estimated that 30 000 congenitally infected infants would be born in the United States in 1980, of which 6000 would be significantly and permanently handicapped with neurodeficiency [18]. Clinically manifest CMV infections are also frequent in immune-suppressed allograft recipients, becoming more important with more intense immune suppression. Thus, CMV infection occurred in 43 (74%) of 58 patients undergoing bone marrow transplantation at The Johns Hopkins Oncology Center. Infection was fatal in 12, non-fatal in 23 and present at death from other causes in 8 [34].

In an American series of 320 renal transplants, CMV infection occurred in 181 of the patients and accounted for 25% of deaths, 20% of graft failures, 30% of febrile episodes and 35% of episodes of leucopenia [20]. It has also been suggested that CMV may be an important factor in the immune suppression that occurs in acquired immune-deficiency syndrome (AIDS), a condition which may progress to Kaposi's sarcoma. The rationales for this suggestion are that more patients with disease have antibody to CMV than controls, that CMV infection is a suppressor of cellular immunity and that DNA and early antigens of CMV have been found in Kaposi's sarcoma cells [10–12].

Since infections in normal subjects are usually asymptomatic, they are not readily amenable to treatment by antiviral drugs and attention has centred on their prevention by the use of vaccines. Strains of live vaccines have been developed but there have been concerns as to the frequency of congenital infection following reactivation of natural infection during pregnancy (a concern supported by the reports of second infected siblings), and anxiety about possible oncogenic effects of CMV itself. Nevertheless, CMV infections are an important target for antiviral chemotherapy, particularly in immune-compromised subjects. Combined treatment with acyclovir and interferon was without effect in the treatment of CMV infections in bone marrow transplant recipients [23], although in a placebo-controlled trial of interferon in the prevention of CMV infections in renal transplant recipients, patients receiving interferon had fewer clinical signs of CMV infection (interferon 1 of 20 patients, placebo 7 of 22 patients; $P = 0.03$) [15].

Epstein–Barr virus

Epstein–Barr virus (EBV) is the cause of infectious mononucleosis or glandular fever. This can be a chronic infection, leading to malaise, fatigue, and bouts of fever over many months. Infections can also reactivate in immune-compromised patients. Epstein–Barr virus appears to be an aetiological factor in the development of Burkitt's lymphoma and nasopharyngeal carcinoma in respectively African and Chinese populations. No vaccines have yet been developed and this virus is another target for chemotherapy.

Viruses causing respiratory illness

Many viruses cause respiratory illness in human subjects (Table 4). Unfortunately, individual viruses are not associated with clear-cut clinical characteristics. Thus, viruses were recovered from between 38% and 69% of children with upper respiratory infections, bronchitis, pneumonia or croup. Influenza, parainfluenza, adeno-, rhino- and respiratory syncytial viruses were recovered in all these clinical entities: although parainfluenza virus predominated in croup, influenza and adenoviruses in upper respiratory infections, rhinoviruses in bronchitis, and respiratory syncytial virus in pneumonia (Table 5). Similarly, in patients with colds, although rhinoviruses predominate, other viruses also occur frequently. In view of the wide range of aetiologi-

TABLE 4

Respiratory tract viruses of man

Genus	Types
Influenza virus	A, B, C
Paramyxovirus	Parainfluenza virus Types 1–4
Pneumovirus	Respiratory syncytial virus (RSV)
Rhinovirus	Over 120 types
Enterovirus	Group A coxsackie 23 types
	Group B coxsackie 6 types
	Echovirus 31 types
	Enterovirus 4 types
Coronavirus	3 types
Mastadenovirus	36 types

TABLE 5

Viruses associated with main categories of respiratory illnesses. Children all ages

	Total	Total virus	Para-influenza (%)	Influenza (%)	Adeno-virus (%)	Rhino-virus (%)	RSV* (%)	Others (%)
URTI	3962	1705 (43%)	12	22	16	7	21	22
Bronchitis	1164	445 (38%)	18	8	9	10	45	9
Pneumonia	555	222 (40%)	13	8	9	5	48	17
Croup	392	246 (69%)	60	9	4	9	14	4

From: Gardner, P.S. Rapid Virus Diagnosis. Virus Diseaes. Ed.: R.B. Heath. Pitman Medical, 1979.
* Respiratory syncytial virus.

cal agents, rapid virological diagnosis will assume considerable importance if virus-specific antiviral drugs become available. Rhinovirus and respiratory syncytial virus are considered further below.

Rhinoviruses

Rhinovirus infections, a major cause of the common cold, are important both economically and because they may precipitate exacerbations of bronchitis, sinusitis and otitis media in predisposed patients. Rhinoviruses can be grown in cell culture but no adequate animal model of infection is available. Although infection with rhinovirus infection could be prevented by a vaccine, the development of a polytypic vaccine to cover the 120+ types is at present impractical.

A number of synthetic compounds have been shown to inhibit rhinovirus in tissue culture but only enviroxime administered simultaneously by oral and intranasal routes has been shown to exhibit some effects in the prevention of experimental

rhinovirus infections in human subjects [31]. Intranasally administered α-interferons are very effective in similarly designed experiments although prolonged treatment causes nasal irritation [32,37]. Rhinovirus infections therefore remain a target for the development of antiviral drugs both for prevention and treatment.

Respiratory syncytial disease

Respiratory syncytial disease is the chief cause of severe and even fatal bronchiolitis and pneumonia in infants. The illness starts as a cold, followed by fever and shortness of breath. The occurrence of unusually severe illness at a time when maternal circulating antibody is still present, suggests that IgG-antibody sensitizes tissues to damage by viral invasion. Infants, who received an experimental inactivated vaccine, also developed a particularly severe respiratory illness following infection. The mechanism for this may be the same as that underlying more severe disease in children with maternal IgG, but may also be related to the fact that, during the inactivation of the vaccine, a particular antigen (the fusion protein) had been destroyed [22]. In view of the inadequacy of vaccines and the severity of the disease, respiratory syncytial disease is potentially an important target for antiviral chemotherapy.

Viruses causing gastroenteritis

In the same way that respiratory illnesses are caused by many viruses, several species, including rotavirus, adenovirus, calicivirus and coronavirus, are involved in gastroenteritis; only rotavirus will be considered further.

Rotavirus

Rotaviruses infect cells lining the small intestine. They occur in many avian and mammalian species including man, where they are responsible for 25–80% of childhood diarrhoeas in different parts of the world. In developing countries, rotaviruses are probably the major cause of diarrhoeal deaths in infancy, with an estimated 1 million fatalities annually. In developed countries infections are rarely fatal, since dehydrated patients are given adequate and timely hospital care. Nevertheless, viral gastroenteritis is second in frequency only to the common cold among illnesses affecting US families. Techniques are available for rapid identification of rotavirus in faeces. Also, suitable systems for growth in tissue culture have recently been found. Rotaviruses have been shown to contain 11 individual segments of double-stranded RNA, each specifying a polypeptide. Genetic reassortants between calf and human rotaviruses have been detected and it may be that rotaviruses have some parallels with influenza viruses in relation to antigenic variability.

Attempts are being made to develop rotavirus vaccines. Some compounds with anti-rotavirus activity have been found [43], and beneficial results from oral administration of gammaglobulin to infected infants suggest that safe and effective agents are likely to be clinically useful [1].

Human papilloma viruses

A number of human papilloma viruses (HPV) have been identified. HPV_1 and HPV_4 are associated with deep plantar warts, HPV_2 with common warts, HPV_3 and HPV_{10} with flat warts, HPV_6 and HPV_{11} with condylomata acuminata, HPV_{11} with laryngeal papillomata, and HPV_5, HPV_8 and HPV_9 with epidermodysplasia verruciformis. HPV have also been implicated as a cofactor in the development of genital cancer [60]. A number of reports indicate that intralesionally or systemically administered interferons are of benefit in the management of patients with laryngeal and genital warts [13,38,39]. While interferons are potent antiviral materials, they also possess other properties, including anticellular and immuno-modulating activities. The extent to which the beneficial effects of interferons in the treatment of HPV infections relate to their non-antiviral properties is not clear. Furthermore, systemically administered interferons regularly cause fevers, chills and headaches. Unfortunately, HPV cannot yet be grown in tissue culture, but compounds with anti-HPV activity would be of considerable interest.

Viral haemorrhagic fevers

The importance of viral haemorrhagic fevers and the prospects for prevention and treatment have been considered in a recent review [17]. Certain of these viruses are targets for antiviral chemotherapy.

Acquired immune deficiency syndrome (AIDS)

The detection, isolation and continuous propagation of cytopathic retroviruses from patients with acquired immune deficiency syndrome [33], leads to the prospect of development of vaccines and antiviral agents for the prevention and treatment of this condition.

General comments

This review makes no claim to be complete. Some important viruses have not been included and new viruses pathogenic to man will continue to be identified. Certain points are worth stressing. Antiviral drugs are unlikely to be of value in treatment, if symptoms only appear with the cessation of virus replication but drugs may be useful in the prevention of infections in contacts. For the vast majority of infections, early treatment is important if it is to be useful. Early treatment demands early diagnosis, either clinically based upon pathognomonic symptoms and signs, or by rapid viral diagnostic techniques. With the availability of specific antiviral compounds, the latter will assume greater importance. Although vaccines or other measures may be highly effective in preventing many infections, it should be remembered that for the patient in whom vaccination is contraindicated or in whom prevention fails there exists an individual need for safe antiviral therapy.

TABLE 6

Some viruses against which specific antiviral agents would be clinically useful

Virus	Licensed vaccine available	Specific immuno-globulin available	Licensed drugs available
Measles	+ (L)	+	-
Rubella	+ (L)	-	-
Influenza A	+ (K)	-	+
Influenza B	+ (K)	-	-
Hepatitis B	+ (K)	+	-
Rabies	+ (K)	+	-
Herpes simplex I & II	-	-	+
Varicella zoster	-	+	+
Epstein-Barr	-	-	-
Cytomegalovirus	-	-	-
Rhinovirus	-	-	-
Respiratory syncytial	-	-	-
Rotavirus	-	-	-
Human papilloma virus	-	-	-

K = killed; L = live.

Table 6 lists viruses and the availability of vaccines, specific immunoglobulins and licensed antiviral drugs for their prevention and treatment. Of the 14 viruses shown, no preventative or therapeutic agents are available against six. Vaccines have been licensed for the prevention of six, and specific antiviral drugs against only three infections. There are clear needs for new or better agents for the treatment and prevention of rhinovirus, influenza, respiratory syncytial and other respiratory viruses, hepatitis B, Epstein-Barr, cytomegalo-, rabies, human papilloma and rotaviruses.

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