Update
Le point

*Articles in the **Update** series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.*

*Les articles de la rubrique **Le point** fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.*

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Approaches to the control of respiratory virus diseases*

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Viruses of various biological types are known to cause a wide range of acute respiratory infections, ranging from mild colds and catarrh to severe bronchiolitis and pneumonia. Bacteria also cause respiratory diseases including serious conditions such as otitis media and pneumonia. The whole situation is complex and to understand the epidemiology we also need to consider nutrition, environment, climate, and chronic diseases. Acute respiratory viral diseases are very common in all areas of the world and contribute to morbidity and probably to mortality. There are no antiviral drugs or vaccines which would be generally useful. It ought to be possible to reduce the effects of these diseases by improving the standard of general management of cases. This would involve careful nursing, administration of appropriate antibiotics, and referral of severe cases to a properly staffed and equipped hospital. Further research is needed to develop ways of doing this and to evaluate the results.

It seems sensible to start this survey by considering what evidence there is that viruses are a cause of acute respiratory infections. A detailed analysis of this subject is to be found elsewhere[a] but the main points are summarized here.

During the last 25 years viruses have been isolated from an increasing proportion of children and adults with acute infections of various parts of the respiratory tract. Thus, in studies made in the United Kingdom, we distinguished diseases with symptoms mainly in the nose (common colds), the throat (sore throat or pharyngitis), the larynx (laryngitis), the bronchi but not the lower airways (bronchitis), and the bronchioles and lung parenchyma (bronchiolitis or pneumonia).[b] The viruses are usually identified by inoculating a variety of tissue cultures with respiratory secretions collected from infected subjects. These cultures are incubated and observed for the development of cell degeneration (cytopathic effect, CPE) or the adherence of red cells (haemadsorption). Further tests on the fluid from the cultures establish whether these changes are due to the presence of viruses, and the viruses themselves are then identified serologically.

The viruses have been found to fall into a number of different biological categories, and some have many different serotypes. The specific details on these points are given in Table 1.

* A French version of this article will be published in a later issue of the *Bulletin*.

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[a] JACKSON, G. G. & MULDOON, R.L. *Viruses causing common respiratory disease of man*. Chicago, University of Chicago Press, 1975.

[b] MILLER, D. L., ed., Acute respiratory virus diseases. A. symposium. *Postgraduate medical journal*, **49**: 749–821 (1973).

Table 1. Some viruses causing important acute respiratory disease in man

Name	Nucleic acid[a]	Symmetry	Envelope	No. of human serotypes
Parainfluenza viruses	RNA negative	helical	yes	4
Respiratory syncytial virus	RNA ?	helical	yes	1
Rhinoviruses	RNA positive	cubic	no	> 100
Coronaviruses	RNA positive	helical	yes	> 3
Adenoviruses	DNA double stranded	cubic	no	Only certain ones cause respiratory disease. Types 1, 2, and 5 are endemic; 3, 7, 14, and 21 are epidemic.
Enteroviruses	RNA positive	cubic	no	> 70

[a] Negative and positive refer to the sense of the strands of the RNA.

THE ROLE OF VIRUSES

The presence of a virus in a patient's throat does not prove that it is the cause of the illness. The evidence for this has to be carefully assessed for each type of virus and for each serotype. The most straightforward test is to culture the virus in the laboratory and then inoculate it into an experimental animal to try to reproduce the disease seen in the patient. However, most laboratory animals are unaffected by the majority of these viruses, and it is necessary, where possible and ethical, to give some of these agents to human volunteers. In this way it has been shown, for example, that volunteers inoculated with rhinoviruses and coronaviruses do develop typical colds identical to those in the patients from whom the viruses were isolated. In cases where the viruses do not readily affect adults, or the disease with which they are associated is observed only in children, we have to argue from epidemiological data only, considering whether the virus is found regularly in patients with a certain disease, and rarely in other subjects in the same community; and whether patients show an antibody response during the disease, indicating the presence of an active infection. These arguments are reinforced if a certain type of virus is found particularly in certain types of disease—parainfluenza viruses in laryngotracheobronchitis and adenoviruses in pharyngoconjunctival fever, for example.

Table 2. Some clinical syndromes induced by respiratory viruses[a]

	Common cold	Sore throat	Croup, laryngitis, tracheitis	Bronchitis	Pneumonia, pneumonitis
Parainfluenza viruses	+		++	+	+
Respiratory syncytial virus	+		+	++[b]	++
Rhinoviruses	+++			+	
Coronaviruses	++				
Adenoviruses	+	++		+	+
Enteroviruses		++			

[a] Influenza virus is not mentioned here though important epidemics occur in all countries of the world. Measles is also excluded as it is usually easy to recognize the catarrhal disease and any subsequent pneumonia by clinical means.

[b] This virus is the main cause of the syndrome of bronchiolitis in infants.

Results of this sort have been carefully evaluated and it is now agreed that many viruses are causally related to specific respiratory diseases. Table 2 summarizes current views. In patients with chronic respiratory disease, such as adults with chronic bronchitis or children subject to asthma or wheezy bronchitis, the same viruses can cause severe relapses or exacerbation of these conditions.[c]

It is possible that vaccination may protect against some of these infections e.g., bronchiolitis of infants, which is caused by respiratory syncytial virus. However, it is unlikely that a vaccine can be produced that will be effective against all of the great variety of viruses involved in acute respiratory diseases. The subject of vaccination will not be pursued further as it will be dealt with in another article in this series.

The next point to consider is the proportion of acute respiratory diseases that are due to virus infection. It is known, for example, that a high proportion of children seen at home or admitted to hospital with acute lower respiratory disease are suffering from virus infections. However, it is often reported that of minor respiratory infections, such as colds, especially in adults, only about 25% yield a virus. This may largely reflect the technical difficulty of collecting suitable specimens and testing them adequately, and in some recent work, it was found that, after exhaustive testing using organ culture and electron microscopy in addition to tissue cultures sensitive to rhinoviruses, about 4 out of 5 patients with mild upper respiratory disease yielded a virus (see Table 3).

Table 3. Results of intensive testing of nasal washings from adults with colds[a]

Results of virus test	No. of specimens	
Rhinovirus isolated	15	25
Coronavirus isolated	7	
Parainfluenza virus isolated	2	
Influenza virus isolated	1	
Produced colds in volunteers	3	
Probably produced colds in volunteers	3	
No colds in volunteers	5	
Total	36	

[a] Larson, H. E. & Reed, S. E. unpublished data, 1980.

Secondary effects of virus infections

Viruses that invade the upper respiratory tract may spread to other sites. A recent paper by Lewis et al. provided data to show that these viruses are among the commonest causes of febrile convulsions, apparently because they disseminate to other parts of the body, including the nervous system.[d] In elderly people, minor respiratory infections are thought to precipitate heart failure in those with diminished cardiac reserve. In children, infection may spread to the lower respiratory tract, which is susceptible to attack by several viruses, e.g., respiratory syncytial virus, parainfluenza viruses, or adenoviruses. It is also important to note that in infants and young children who are inadequately fed an attack of upper respiratory infection may be sufficient to precipitate acute nutritional failure (R. Whitehead, personal communication, 1974).

[c] TYRRELL, D.A.J. Respiratory viruses—some recent advances. In: Heath, R.B., ed., *Virus diseases*. Tunbridge Wells, Pitman Medical, 1979, pp. 3–7.

[d] LEWIS, H. ET AL. The role of viruses in febrile convulsions. *Archives of disease in childhood*, **54**: 869–876 (1979).

THE ROLE OF BACTERIA

It is widely believed that bacterial infections commonly follow virus infections or may occur at the same time. Although there is evidence that influenza virus infections predispose to infection with staphylococci or pneumococci there is little evidence that this is true of other virus infections. Bacteria are known to cause pneumonia, acute sinusitis, or otitis media, and to contribute to exacerbations of chronic bronchitis and these diseases may occur after minor respiratory virus infections. However, observed symptoms may be a result of a damaged and malfunctioning mucosa rather than a superadded bacterial infection, since the mucous membranes can take a long time to recover from the damage that occurs when viruses replicate in the epithelial cells lining their surface. Nevertheless, there is no doubt that virus infection can impair some of the mechanisms that protect the airways from bacteria—the clearance of particles by the 'mucociliary escalator' is a good example. Invasion by bacteria can also be assisted by other factors, e.g., chilling, alcohol, or malnutrition, which increase susceptibility by impairing a variety of antibacterial mechanisms. Much more research is still needed on the identification of the viruses or bacteria responsible for serious respiratory conditions especially in the developing countries.

FACTORS AFFECTING MORBIDITY

The incidence of respiratory virus infections varies with the season. In temperate climates the rate increases as the cooler autumn weather develops and declines again as spring passes into summer, while in other areas the incidence may fluctuate with the wet and dry seasons. In spite of these differences in timing it seems that the overall frequency of diseases such as colds and sore throats is similar in tropical and temperate areas,[e] and antibodies against the common respiratory viruses are found in all areas of the world. Only extreme physical isolation seems to restrict the circulation of these organisms; the inhabitants of Tristan da Cunha, for example, were apparently very little exposed to respiratory viruses and suffered badly from this type of infection when they were evacuated to Britain. Similar outbreaks seem to have occurred when isolated tribal peoples were first contacted by outsiders.

Depending on the criteria used it is known that, on average, adults have from 2 to 5 acute respiratory illnesses each year, and children generally have more. Almost all are probably due to viruses and a high proportion do not require medical attention. Only in young children and old people are these illnesses dangerous, but they interfere with work, education, and social life at all ages.

In developed countries in the last century, acute respiratory illnesses, many of which progressed to pneumonia, caused a substantial number of deaths in childhood. The incidence has since declined steadily, however, mainly as a result of improved social conditions and better nutrition which have led to a decrease in the amount of infection transmitted and an improved response to infection by the host. More recently, antibacterial drugs and improved paediatric care have no doubt helped, but, as yet, no form of specific antiviral prevention or treatment is available.

It is often not realized that acute respiratory diseases are also a common cause of death in tropical and subtropical areas and in developing countries.[f,g] In order to improve treatment

[e] SUTTON, R. N. P. Minor illness in Trinidad: a longitudinal study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **59**: 212–220 (1965).

[f] COCKBURN, W. C. & ASSAAD, F. Some observations on the communicable diseases as public health problems. *Bulletin of the World Health Organization*, **49**: 1–12 (1973).

[g] COCKBURN, W. C. The importance of infections of the respiratory tract. *Journal of infection*, **1**: suppl. 2, 3–8 (1979).

of these cases, much more information is needed on the pathogenic agents most often involved and the factors that encourage the transmission and increase the effects of the viruses. In view of this, the World Health Organization is assisting in the development of a methodology whereby countries could undertake the necessary multidisciplinary collection and analysis of data.[h] Recently introduced techniques for rapid viral diagnosis, based on detection of viral antigens in respiratory secretions, will be very useful in this respect.[i,j]

CURRENT STATUS OF ANTIVIRAL MEASURES

Much research has been done on antiviral vaccines, and this will be reviewed in a later article in this series. However, so far there is no vaccine that can be used in clinical practice to influence either the mass of disease in the general community, or the severe illnesses caused by respiratory syncytial and parainfluenza viruses in children. The latter have been recognized for years as diseases that might be dealt with by vaccination.

The progress of research on antiviral drugs has been very slow,[k] but we know now that it is possible in principle to treat virus infections with drugs given either systemically, e.g., amantadine in influenza A, or locally, e.g., idoxuridine in herpes simplex infections of the eye. Research on interferon has shown that there are substances that are relatively non-toxic and active at very low concentrations against a wide range of viruses. Other synthetic antiviral drugs of even greater activity and lower toxicity are being developed, but they are often active only against certain strains of one biological type of virus. There are therefore grounds for optimism but it will be years before we know whether these new substances are clinically useful. In the meantime, it is important to ensure that all patients receive the most appropriate treatment.

Principles for a scheme of management

Most viral infections, and some bacterial infections, are self-limiting and do not require antibacterial treatment, though symptomatic treatment is desirable. It is sad that in many places patients with simple viral infections are given expensive vitamins, mixtures of symptomatic remedies, and even antibiotics, when often the money would be better spent on food, clothes, or general amenities.

If the symptoms and signs suggest a bacterial disease such as pneumonia or otitis media, then an antibacterial drug should be given. The patient also needs appropriate nursing and general care—plentiful fluids by mouth, sponging and antipyretics to control fever, moist smoke-free air, protection from overheating or chilling, and good food as soon as he is able to eat again. The patient's attendants need to know when further help should be sought, for instance if a child shows convulsions or respiratory distress or if there is a lack of response or delayed recovery. In patients severely ill with bronchiolitis, for example, good management of physiological function in hospital can be life-saving.

Such a scheme should be applicable anywhere from a city suburb to a poor rural village, and could be adapted and expanded to meet a variety of local situations. A series of studies should be made to evaluate the use of such schemes in various environments. In the first place, one might check whether a simple set of rules or guidelines would in fact ensure that

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[h] WHO Technical Report Series, No. 642, 1980 (*Viral respiratory diseases:* report of a WHO Scientific Group).

[i] *Manual for rapid laboratory viral diagnosis.* Geneva, World Health Organization, 1979 (Offset Publication, No. 47).

[j] Detection of antigens and IgM antibodies for rapid diagnosis of viral infections: a WHO Memorandum. *Bulletin of the World Health Organization*, **57**: 925–930 (1979).

[k] MERIGAN, T. C., ed., *Antivirals with clinical potential.* Chicago, University of Chicago Press, 1976.

each patient got the right treatment—this would require a detailed study of the viruses and bacteria found in a series of patients being managed in this way. It would also be important to investigate whether such a management scheme would, in fact, give good results, particularly in reducing mortality and complications. Although to achieve this one would need an extensive multidisciplinary study, it seems that the time is now ripe for a pilot study to begin. If successful, it could lead to other more detailed studies on the basis of which firm recommendations could be made and a general scheme improved and adapted to local needs. In this way it may be possible to reduce the mortality rates in many areas.