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The WHO Programme for Prevention and Control of Viral, Chlamydial, and Rickettsial Diseases

Brief Review

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Summary

Through the advancement of biological and medical sciences and the application of modern technology, the disease burden imposed by viral, chlamydial and rickettsial disease has steadily decreased. Smallpox has been eradicated, poliomyelitis is under control in many countries, and measles, mumps and rubella viruses may eventually be eliminated in many developed countries. New and improved vaccines have also recently become available for rabies and hepatitis. These are major advancements. Not to be overshadowed however, are the developments which may lead to the prevention or control of other infectious diseases.

For many agents, recently acquired knowledge relating to virology, replication, structural and genetic characteristics, and host responses to infection pave the way for disease intervention in numerous ways. For other agents, recent advances in molecular biology make possible new classes of effective vaccines. It is crucial that these advances be incorporated as soon as possible into effective public health programmes for developing as well as developed nations. Much work yet remains, particularly in the prevention and control of respiratory diseases, diarrhoeal diseases, vector-borne diseases and hepatitis.

The WHO Viral Diseases Programme has a major role in supporting laboratory and field research on new technologies and intervention strategies, in disseminating technological advances through teaching and training, and in translating the newer knowledge into action programmes for the prevention and control of viral, chlamydial and rickettsial diseases.

Introduction

In November 1981 a meeting of Directors of the WHO Collaborative Centres for Virus Reference and Research was held in Geneva. This paper is based on a

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report of that meeting. Inevitably a paper of this brevity cannot include all the matters discussed.

Communicable diseases continue to contribute greatly to morbidity and mortality in all countries and absorb a high proportion of health resources. Improvements in the prevention and control of these diseases are universally important and may be a requirement for economic advancement of many developing countries. Through its technical units and health care programmes, WHO plays a leading coordinating and supportive role in the diagnosis, surveillance and prevention of communicable diseases and improving standards of patient care.

The infectious agents which are included in the WHO Viral Diseases Programme constitute a large proportion of the international burden of disease. This report deals with major elements of the Programme, emphasising developments expected in the period 1984—1989 in terms of:

the major challenges presented by viral, chlamydial and rickettsial diseases, the emerging technologies which may be harnessed to meet the challenge, and the organization and functional aspects of the Virus Diseases Programme.

Virus Disease of Public Health Importance

The status and trends of the most important viral, rickettsial and chlamydial diseases are summarized below:

Viral Gastroenteritis

Acute viral gastroenteritis is a major cause of morbidity and mortality (1). In developing countries it is responsible for 30 per cent of deaths in infants. Rotaviruses are responsible for some 40 per cent of cases and a group of morphologically related viruses (27 nm in diameter), represented by Norwalk virus is also important. Coronaviruses, non-cultivable adenoviruses, calici viruses and astroviruses have also been implicated. Direct electron-microscopy of faecal samples is important in diagnosis.

Rotavirus causes disease almost exclusively in children below the age of six years, those between 6 months and 3 years being the most severely affected. Outbreaks have occurred in neonatal nurseries. Transmission is normally by the faecal-oral route. At least three serotypes have been distinguished and analysis of viral RNA also aids the differentiation of strains. Vaccines are being developed, assisted in part by WHO.

Norwalk and related viruses have caused outbreaks of gastro-enteritis in the United States, Britain, Japan and Australia. Their importance in developing countries is not yet fully established though there is seroepidemiological evidence of frequent infection.

Corona-like particles have been detected by electron-microscopy in the faeces of children and adults with acute and chronic diarrhoea in both developed and developing countries but it is not certain that they cause diarrhoea in their own right.

Astroviruses, caliciviruses and adenoviruses have been detected by electron-microscopy in the faeces of children or adults with diarrhoea in many parts of the world. Although these agents have been implicated in several well documented outbreaks of disease, their overall significance remains to be established.

Poliomyelitis and Some Other Diseases Caused by Enteroviruses

Poliomyelitis of types 1, 2 and 3 are the main causes of paralytic poliomyelitis in man. Vaccination programmes with live or inactivated vaccine have been effective in many countries but in a number of developing countries in tropical and semi-tropical areas the disease has not yet been brought under control and extension of the WHO immunization programme for poliomyelitis is required. In those countries where vaccination has been effective, systematic vaccination programmes are essential to maintain immunity at a satisfactory level.

Enterovirus 71, several echo and coxsackieviruses have been shown to be responsible for poliomyelitis-like syndromes. Some coxsackieviruses have caused pleurodynia and myalgia and other diseases. Enterovirus type 70, and to a lesser extent coxsackie A24 virus, have produced haemorrhagic conjunctivitis.

Virus Infections of the Respiratory Tract

In areas where diarrhoeal diseases are being controlled, respiratory tract infections, particularly pneumonia, have emerged as the main cause of death in children. Viruses are important causes of these infections, and WHO has collaborated with health workers and virologists in several areas in setting up studies on the etiology, management and outcome of cases.

Influenza viruses types A and B are the most intensely studied agents in this group and are known to produce excess mortality during epidemics. The parainfluenza viruses are an important cause of bronchitis and croup. Respiratory syncytial virus is a major cause of bronchiolotis, especially in very young babies. Adenovirus, enterovirus, rhinovirus, coronavirus (2), chlamydia, Rickettsia burnetii and Mycoplasma pneumoniae also cause respiratory illnesses. Vaccines have been developed only for the influenza viruses but work is under way with resperatory syncytial virus and other agents.

In the developed world, influenza is lethal, predominantly among the older age group. The impact of influenza in the developing world is less well understood. Although influenza epidemics during the last few years have been relatively mild, the unique capacity of the virus to produce new antigenic variants of high epidemic potential is well recognized. These changes are monitored by the international network of WHO laboratories, and these are, and continue to be reflected in the maintenance of a high level of surveillance at the national level Attempts to develop more effective vaccines should be encouraged, possibly using DNA recombinant techniques.

Viral Hepatitis

The most important agents are hepatitis A virus (family: picornaviridae), hepatitis B virus, and a third category of at least three as yet uncharacterized agents which cause disease (non-A/non-B hepatitis) (3).

The incidence of infection with hepatitis A virus varies from nearly 100 per cent in developing areas of Asia and Africa to as little as 10 to 20 per cent in Scandinavia. Improvement in standards of hygiene has been associated with decline in the incidence of hepatitis A. Case fatality of adults admitted to hospital is less than 1 per cent and chronic sequelae are rare.

Recent success in cultivating hepatitis A virus *in vitro* has led to the production of experimental inactivated and live virus vaccines which may permit future prevention on a wide scale. Hepatitis B virus is a cause of infection on a global scale and is associated with serious sequelae, including primary hepatocellular carcinoma. Approximately 10 per cent of infections with hepatitis B virus result in persistent viraemia and there are estimated to be about 200 million persistent carriers in the world. Hepatitis B is not transmitted by the faecal-oral route but by contact with blood or other secretions from persistent carriers as well as by the sexual route. Perinatal transmission from pregnant persistent carriers to their offspring is important in Asia. In South-East Asia, China and tropical Africa the prevalence of infection may reach 80 to 95 per cent by adult life with frequencies of chronic viraemia between 5 and 20 per cent; infections in infancy and early childhood predominate. In the Middle East and Central and Eastern Europe, 25 to 60 per cent of adults have been infected and the prevalence of chronic viraemia is 2 to 7 per cent. In North America, Western Europe and Australia the frequency of infection varies from 4 to 20 per cent, prevalence of chronic viraemia is less than 1 per cent and infection before adolescence is rare.

The recent introduction of hepatitis B vaccines (HBsAg) and the availability of high-titred hepatitis B immunoglobulin promise some measure of control. The newer biochemical and DNA recombinant technologies may allow the development of better vaccines.

Non-A/non-B hepatitis is a diagnosis of exclusion when infection by the viruses of hepatitis A and hepatitis B have been ruled out. The blood-borne form occurs throughout the world and a water-borne form has, so far, only been reported from India. Probably at least three viruses are concerned and these are the most common cause of hepatitis arising from administration of blood or blood products from donors free of hepatitis B virus. They are also important in causing adult hepatitis in general and in cases of persistant hepatic dysfunction.

Exanthematous Diseases

Measles virus can be particularly serious in young children and those suffering from malnutrition. A measles virus vaccine now offers control but problems have been encountered with the use of the vaccine in tropical countries, partly because of failures in the preservation of the vaccine. Vaccines with improved thermostability have now been developed.

An attenuated rubella virus vaccine is available to protect against infection in pregnancy.

Chickenpox is usually a mild disease in children, except in the immunosuppressed. In adults it can cause broncho-pneumonia. An attenuated varicella-zoster vaccine is now available for clinical studies.

Viral Haemorrhagic Fevers

Several viruses, most of which are transmitted by insects or rodents, can cause a life-threatening haemorrhagic syndrome, leading rapidly to circulatory collapse and terminal shock. Very often outbreaks occur in rural areas where public health structure is not well defined. Control requires a pooling of resources on an international basis.

Dengue haemorrhagic fever was first recognised in 1956 in the Philippines and has since spread widely in South-East Asia and the Western Pacific causing more than 350,000 cases and 12,000 deaths. In 1981 it caused 158 deaths in Cuba. WHO is supporting a live attenuated vaccine development project.

Yellow fever virus is transmitted from monkeys to man in the Central Americas and in tropical Africa. The reinfestation of several Central American cities by *Aedes aegypti* in the last 20 years may lead to resurgence of urban epidemics. In Ethiopia the disease killed between 15,000 and 30,000 patients in 1960—1962. A safe and efficient live, attenuated vaccine is now available.

Rift Valley fever is enzootic in Central Africa. In 1977 and 1978 it caused serious epidemics in Egypt (4). An effective vaccine is available in limited quantities. The virus of Crimean-Congo haemorrhagic fever, first described in Eastern Europe and U.S.S.R., is widespread in the Middle East and Africa. Omsk haemorrhagic fever is limited to certain regions of the U.S.S.R.

Lassa fever is so far restricted to Africa, south of the Sahara (5). Virus is transmitted to man by direct or indirect contact with the African field rat *Mastomys natalensis*. Argentinian haemorrhagic fever and Bolivian haemorrhagic fever are prevalent in parts of each country. Rodent control measures have been successful in Bolivia. Marburg virus first caused an outbreak of severe haemorrhagic fever in Europe and in 1975 and 1980 it reappeared in South Africa. Ebola virus was identified in 1976 when it caused severe outbreaks in Southern Sudan and Northern Zaire. The animal reservoir for these two viruses is still unknown. A causative virus (Hantan virus) has recently been isolated from haemorrhagic fever which occurs in the Eastern U.S.S.R. and China, Japan and Korea. The natural host of the virus is a field rodent, *Apodemus agrarius*. Apparently the virus is related to the cause of a haemorrhagic fever in Scandinavia.

Encephalitis

The arborviruses (Togaviridae, Bunyaviridae) are normally enzootic but occasionally epidemic in character. Most have a restricted geographical distribution.

Eastern and Western and Venezuelan equine encephalitis viruses, St. Louis virus and members of the California encephalitis group occur in the Americas, tick-borne encephalitis in Europe, West Nile virus in the Eastern Mediterranean and Japanese encephalitis virus and the Australian encephalitis virus (Murray Valley encephalitis virus) in Asia and Australia are the better known examples. Vaccines for some of these are useful in control but more important measures depend on vector control.

Rabies virus (Rhabdoviridae) is perhaps the commonest cause of fatal encephalitis in man in several developing countries. Certain chronic diseases may present as encephalitis, for example, subacute sclerosing panencephalitis.

Sexually Transmitted Diseases and Perinatal Infection (Including Mycoplasma and Chlamydiae)

Sexually transmitted diseases are widespread and common throughout the world, afflicting mainly adolescents and young adults in all social and economic strata. The incidence has increased in the wake of recent social changes and an increasing proportion of these infections are of viral origin.

The Chlamydiae are obligate intracellular micro-organisms. Cell culture techniques have demonstrated that chlamydiae trachomatis, which is responsible for trachoma, is also of considerable importance in genital infections. It is probably a major cause of non-gonococcal urethritis in the male and cervicitis, salpingitis and pelvic inflammation in the female. Post-partum endometritis, perihepatitis and infertility are other possible complications. Studies have indicated that 1 to 7 per cent of healthy men have urethral infection with C. trachomatis and as many as 5 to 20 per cent of asymptomatic women examined in clinics for sexually transmitted diseases have cervical infections. Chlamydial infections transmitted to the infant during birth may affect 1 to 3 per cent of infants. Apart from inclusion conjunctivitis, pneumonia, otitis and myocarditis may result. The causative agent of lymphogranuloma venereum is antigenically related to C. trachomatis but it is biologically different and more invasive.

Mycoplasma hominis and Ureaplasma urealyticum have been implicated as causes of non-gonococcal urethritis and pelvic inflammatory disease.

The two herpes virus types HSV-1 and HSV-2 are closely inter-related antigenically. HSV-1 infection is found predominantly in lesions of the lips, face and non-genital sites, whereas HSV-2 virus is found predominantly in the genito-anal area and in some countries patients with genital herpes account for up to 8 per cent of patients attending venereal disease clinics. An important consequence of genital HSV infection is neonatal infection with herpesvirus.

The sexual route ranks with perinatal spread as one of the main methods of transmission of hepatitis B virus.

The role of sexual transmission of cytomegalovirus in the genesis of congenital infections requires further definition. Primary cytomegalovirus infections, acquired just before or during pregnancy, carry a high risk to the developing foetus.

Nosocomial Viral Infections

These are most obvious in developed countries but may constitute even greater problems in developing countries. Haemorrhagic fevers such as Lassa, Ebola and Crimean-Congo fevers, have caused striking outbreaks with case fatality rates as high as 50 to 80 per cent.

Rotaviruses are known to be particularly important in causing outbreaks of diarrhoea among babies in special care units. However, enteroviruses, such as Echo 11, have spread among infants resulting in serious illness and even death. Measles and chickenpox are a particular hazard in immuno-compromised or immuno-supressed children in hospital.

Influenza has been responsible for many hospital ward outbreaks, particularly among geriatric patients, who are especially vulnerable.

In immunosuppressed patients, reactivation of herpes viruses is a common occurrence. This may have serious consequences with the development of cytomegalovirus, pneumonia, generalized herpes simplex or zoster.

Hepatitis B is a significant occupational hazard to hospital staff who are in contact with blood or secretions from patients.

In opthalmology clinics adenoviruses are a special risk.

Rickettsial Diseases

Louse-borne typhus is the only rickettsial disease that has the potential for explosive epidemics in man. The human body louse is the vector of the causative agent *Rickettsia prowazekii*. The disease continues to be a problem, particularly in the highlands of some countries of Africa, Central and South America. Over the last seven years in Africa, the greatest number of cases were reported from Ethiopia, over 17,000 cases during 1979 (6).

Murine (flea-borne) typhus has a wide distribution throughout the world, and its importance as a human disease is probably much underestimated. Scrub typhus occurs in wide areas of the world where the enzootic cycle of *R. tsutsugamushi* is now known to extend.

Q fever occurs sporadically throughout the world, ranging in severity from subclinical infection to serious chronic disease. Acquisition of infections usually occurs by respiratory inhalation of infective aerosols from domestic livestock. Sporadic cases of tick-borne spotted fever are common wherever man is exposed to ixodid ticks infected with pathogenic rickettsiae. Of all the members of this group, Rocky Mountain spotted fever can be the most virulent.

Prevention of tick-borne rickettsial diseases depends on vector control.

Application of Techniques for Surveillance, Management and Control of Viral Diseases

The Changing Emphasis of Technology

Traditional diagnostic methods are the isolation of a causal virus or the finding of a rising titre of specific antibody. To these have been added recently a number of other, and often more sensitive, methods, some of which have yet to be fully exploited. These newer methods include electron microscopy, including immune electron microscopy, when large numbers of viral particles are present, radio-immune assay (RIA) and enzyme linked immunosorbent assay (ELISA) (10) to detect small concentrations of viral antigen, nucleic acid hybridization to detect small quantities of nucleic acid in infected cells, and immunofluorescence to detect virus infected cells. The detection of specific IgM antibodies in single serum specimens helps early diagnosis. Other methods, such as tests for viral enzymes, are being developed.

Biotechnology has provided two methods which have proven their worth and will make an even greater impact in the future. Hybridoma techniques (11) provide specific monoclonal antibodies of unique value in detecting and defining single viral antigens and since hybridoma cells can be stored in liquid nitrogen, and also reproduce indefinitely, they provide an inexhaustible supply of identical molecules of antibody (7, 8) or other substances (e.g. pure interferons).

Such pure antibodies can be used not only in single diagnostic tests (9) but also in the more sophisticated detection of immunogens in vaccines, as well as in research on structure and function of viruses. *In vitro* hybridoma techniques may significantly reduce the need for laboratory animals. DNA recombinant technology allows both the production of vaccines for viruses which are either not yet cultivable or are highly pathogenic for laboratory personnel, and also the production of critical viral antigens for use as vaccines. The use of this technique in research has yet to be fully exploited, e.g. in the detection of integrated viral nucleic acid in cells (12).

Current Techniques for Virological Diagnosis and Surveillance

The newer diagnostic methods have been applied as follows (13). In respiratory infections with respiratory syncytial virus, influenza and parainfluenza viruses, adenoviruses and measles, viral antigens can be detected within cells in the nasopharyngeal secretions by immunofluorescence, or less commonly, ELISA techniques.

Most viruses causing gastroenteritis have not yet been cultivated. Some are detected by direct electron microscopy, and ELISA and RIA methods are useful where reagents are available, e.g. with rotaviruses and Norwalk and related agents.

Among the exanthemata, the detection of specific IgM antibodies is used for diagnosis of rubella (14) and measles. The electron microscopy of vesicle fluid differentiates herpes from the poxviruses, and immunofluorescence can be used after crusts have formed.

The detection of IgM in acute phase sera, and the indirect immunofluorescence test, perhaps using monoclonal antibody, have been useful in diagnosis of some encephalitides e.g. herpes, Rift Valley fever, Japanese B, and poliomyelitis. Such techniques should be developed for application to other encephalitides (St. Louis) and to certain haemorrhagic fevers (eg. Marburg, Ebola).

Hepatitis A can be diagnosed by the detection of IgM in early sera. Hepatitis B can be diagnosed by detection of HBsAg or specific antibody. The HBsAg assay is the most important single method of recognising both acute and chronic infections and can be detected by several techniques including ELISA, RIA and reverse passive haemagglutination. DNA hybridization is a new and promising diagnostic method.

The immunofluorescent technique is very sensitive in determining serotype specificity of the chlamydia. However it is of more use in first attacks of urethritis and not so useful when applied to a high risk population against the background of previous chlamydial attacks. Simple procedures of detection of chlamydiae by direct examination of patients' tissues are urgently needed.

For the rickettsial diseases the most useful of the newer techniques for sero diagnosis are probably those based on indirect immunofluorescent antibody assays.

The WHO Viral Reagents Programme

For the success, particularly of these newer techniques, it is essential to have adequate supplies of satisfactory pure reagents. One of the priorities of the WHO virus diseases programme is to stimulate and encourage the production

control and distribution of such reagents. Hybridoma techniques will probably be increasingly used in the production of monoclonal antibodies as pure specific diagnostic reagents. It is recommended that WHO should take an active role in the coordination of studies to determine the usefulness of monoclonal antibodies in the various potential fields of application and in the selection of individual Preparations for routine use as reagents. This could involve the coordination of international collaborative studies to compare possible reagents available now and in the future. Similar considerations apply to reagents used in DNA recombinant technology although these at present are less fully developed.

Immunoprophylaxis and Immunotherapy of Virus Diseases

It has already been indicated how the newer techniques developed for diagnostic testing can also be useful for the efficient production of better quality vaccines. The development of synthetic vaccines using these techniques points to the ultimate goal of chemically specified multivalent vaccines. These may ultimately replace many of the currently used bacterial and viral vaccines which often contain much irrelevant proteins and other material which contaminate the essential immunogen and which may lead to unwanted side effects.

One of the fields of current interest is the development of viral vaccines containing purified 22 nm HBsAg particles, derived from the plasma of persistent human carriers of hepatitis B, and the possibility that such vaccine components can eventually be produced by E. coli or yeast cells.

Human immunoglobulin has been effective in passive prophylaxis against a number of diseases, for example, hepatitis B, varicella-zoster and possibly some of the haemorrhagic fevers. Monoclonal antibodies of human origin could in the future be used for the prevention and treatment of these and other virus diseases. Human monoclonal antibodies might also be of value if they could be attached to drugs or toxins. Such reagents would have a special affinity for specific virus infected target cells in patients with chronic viral diseases.

Chemoprophylaxis and Chemotherapy

Despite early doubts, it is now clear that several steps of viral multiplication are vulnerable to attack by drugs for example, an early stage, probably the uncoating of RNA of influenza A virus, is inhibited by amantadine and its derivatives, and the synthesis of herpes viral DNA by the virus induced DNA polymerase is inhibited by acyclovir.

Adenine arabinoside has been shown to be effective against herpes encephalitis.

Acyclovir (acycloguanosine), bromovinyl deoxyuridine (BVDU) and fluoroiodocytosine (FIAC) appear to be more potent and more selective in their antiviral action than the previous anti-herpes drugs, idoxuridine, trifluorothymidine and adenine arabinoside. These drugs hold promise for local and systemic therapy of herpes simplex and varicella zoster.

Phosphonoformic acid, the less toxic analogue of phosphonacetic acid, inhibits the DNA polymerase of herpes viruses and thereby viral replication. Its good therapeutic activity in animal models and lack of dermal toxicity makes this compound promising in the topical treatment of labial and genital herpes.

Amantadine hydrochloride and a closely related analogue, rimantadine, are effective against influenza A. Rimantadine is rather less toxic for the CNS and is widely used in some areas. Studies comparing these two drugs for prophylaxis and therapy are in progress.

Interferons (IFNs)

Interferon might alter cellular regulatory mechanisms and with certain viruses prevent the translation of viral messenger RNA into viral peptides.

Using recombinant DNA technology it has been possible to clone the genes of human interferons (IFNα, IFNβ and IFNγ). These DNAs have been sequenced; there are over twelve distinct genes for IFNα, presumably each coding for a distinct molecular species of IFNα. Large quantities of at least one of these molecular forms of IFNα have been produced by gene expression in bacterial cells, enabling clinical trials of its antiviral activity to be performed. This represents an enormous technical advance.

Controlled trials have shown that sufficient doses of potent IFNs are of therapeutic benefit in immunosuppressed patients with generalized herpes zoster. It has also been shown that experimental rhinovirus may be prevented by local IFN. Treatment with potent IFN has been shown of value in chronic hepatitis B infections, particularly if combined with adenosine arabinoside. The purified interferon preparations are not free from toxic effects however. IFNs produced in mammalian cells have produced local inflammation and systemic effects such as fever, headache, malaise, tachycardia and changes in polymorphonuclease and lymphocyte counts.

In future trials, the local treatment of respiratory virus infections of the upper and lower respiratory tract and herpes virus infections of the cornea should be studied.

The screening of many molecular species of interferon for clinically useful properties, e.g. penetration of CNS and freedom from toxicity will be an important element of future research work.

Organization and Function of the WHO Programme on Viral, Chlamydial, and Rickettsial Diseases

The WHO Collaborating Centres for Virus Reference and Research form the backbone of the programme on viral diseases and enable WHO to expand its effectiveness beyond its own limited resources.

These centres identify and classify viruses, and maintain and distribute stocks of viruses, antisera and other reagents. They collect epidemiological data for WHO. They train virologists. They institute collaborative research. They advise other national laboratories and on request assist and advise during epidemics. They advise WHO on its programmes. Each centre reports annually to WHO, and periodically (e.g. every three years) the work and quality of each centre is evaluated by WHO. New centres are set up or designated as new technologies develop. A present there are 71 collaborating centres for virus reference and research, 101 national influenza centres, 45 national centres for hepatitis, 5 national centres for enteroviruses, one national centres for rapid laboratory viral diagnosis and 3 national centres for interferon. Frequent cooperation and con-

sultation between centres is emphasised, particularly but not exclusively within each special field (e.g. influenza research). The national centres also provide close links with local and national health authorities, faster early recognition and better understanding of local viral disease problems and open opportunities to improve primary health care.

Collaborative Scientific Research Relevant to the Virus Diseases Programme

Particularly through national centres, WHO stimulates and supports fundamental and applied research in virology and related fields and the application of newer techniques to the improvement of diagnosis, epidemiological work, prophylaxis and therapy. Among appropriate areas of research are those directed towards improvement in the sensitivity, reliability, specificity and field of application of diagnostic techniques; advances in techniques available for epidemiological surveillance and improvements in methods for the interpretation of data; progress in the understanding of the genetic basis of viral virulence and persistence of the mechanism of viral pathology; advances in knowledge of the immunological responses to viral antigens and of their contribution to protection against disease; the better design and use of viral vaccines, including the use of immunological potentiators, and the prevention and treatment of viral diseases by antiviral compounds, including interferons and monoclonal antibodies.

We give some examples: DNA recombinant techniques enable analysis of viral genomes and so facilitate understanding of the genetic basis of viral virulence. Again the preparation of specific viral antigens by cells bearing cloned copies of viral genomes may enable the preparation of antigens for viruses which cannot be propagated *in vitro*, as is the case with hepatitis B virus.

Vaccines elicit the production of specific immunoglobulins and a variety of cellular immune responses. WHO can support collaborative field studies of vaccine efficacy to help elucidate the relative roles of these several types of response.

Etiologic diagnosis of viral diseases is important for patient care, epidemiological study and the control of infectious disease. The improvement of diagnostic methods is therefore encouraged by WHO. WHO has supported the production of laboratory manuals, containing detailed descriptions of techniques for diagnosis of specific viral diseases. These manuals require constant review and updating. Workshops have been held in the fields of influenza, other respiratory diseases, hepatitis, rotaviruses, dengue, poliomyelitis and measles during the past decade. Essential aspects of the Workshops are instruction in the appropriate use of WHO. reagents, selection of suitable methods and critical evaluation of data. The laboratory manuals are designed in part to provide technical guidance during Workshops. Supply of disposable equipment for specialised techniques and reagents for a period until these become available locally is an important part of the follow-up of Workshops and should be accompanied by quality control of locally produced reagents and test results.

Development, Production and Distribution of Viral Reagents

Of crucial importance to the effectiveness of the virus diseases programme is the availability to National laboratories of high quality reagents. In many cases the preparation of reagents is best done by specialised laboratories; however the

selection and establishment of reagents suitable for international use requires extensive collaborative studies involving several WHO collaborating centres.

Three categories of reagent are used in the WHO programme. These are:

a) Working reagents are those required for diagnostic or other purposes where they are not readily prepared by national laboratories. Examples are pools of enterovirus antisera for the typing of echoviruses and coxsackie viruses, specific immune sera for use in the direct diagnosis by immunofluorescence of respiratory virus infections and antisera for the detection and identification of hepatitis antigens.

b) Reference reagents are provided to national laboratories to facilitate the control of locally prepared working reagents. Among WHO reference preparations are prototype virus strains for many of the major groups of viruses and specific immune sera for many virus strains.

c) International biological standards are essential for the standardization, measurement and control of viral vaccines.

The provision of reagents has an especially important role in the WHO influenza programme. The unique antigenic variability of this virus necessitates constant revision of reagents suitable for the identification of currently prevalent influenza A and B viruses. Each year an updated kit of reagent is provided to each national influenza centre and additional reagents are distributed immediately on the appearance of new variants. In addition reference haemagglutinin antigen preparations and corresponding antihaemagglutinin sera are provided for the standardization of the potency of inactivated influenza vaccines by immunoassay methods.

The establishment of a programme on the diagnosis of viral infections by direct rapid identification of viral antigens or the detection of IgM antibody responses provides a need for specialised reagents. This is a rapidly developing field and in the next few years many additional tests will probably become available.

For the purposes of direct viral diagnosis the reagents used should have been subjected to quality control studies involving two or more collaborating laboratories to prove their value for routine use. WHO collaborating centres for reference and research play an important role in testing reagents and establishing the suitability of test systems and these laboratories should continue to cooperate with WHO in the preparation and distribution of reagents which are considered essential for major public health problems.

Monoclonal antibodies, used singly or as mixtures, have an important potential role as standard reagents for virus diagnosis, epidemiological research and the production and control of vaccines. Numerous monoclonal antibody preparations against the antigens of several viruses are already available. The rapid proliferation of these reagents will potentially lead to confusion and WHO should take a lead in coordinating collaborative studies on the specificity and potential uses of these reagents for reference and diagnostic purposes.

DNA recombinant techniques are now available which enable the preparation of large quantities of DNA of uniform and well defined molecular composition, representing partial or complete copies of gene sequences on virus genomes.

WHO should prepare and distribute appropriate DNA reference reagents for use in genetic studies. DNA recombinant techniques are also potentially of great value for preparing on a large scale working or reference reagents containing specific, reproducible and uniform preparations of virus antigens for diagnosis, surveillance and research. WHO, in consultation with the collaborating centres for reference and research should consider the exploitation of these methods in order to extend and improve the reagent programme.

Reporting of Epidemiological Information

The effective and rapid communication of information on epidemiological events is an essential part of the WHO viral diseases programme and epidemiological reports to WHO can be published in the WHO Weekly Epidemiological Record. Where a rapid response to epidemiological information is desirable, the application of new techniques should be explored, for example, facsimile transmission techniques with telephone networks.

WHO also prepares annual reports on the frequency of virus disease diagnoses, which are distributed to the Collaborating Centres for Reference and Research and other centres. In addition, the epidemiological and virological data bank is accessible to participating laboratories. These data may be helpful to national authorities when assessing local programmes. WHO Collaborating Centres for Reference and Research working in the same field should regularly exchange up to date epidemiological information among themselves and with WHO.

Emergency Assistance in Epidemics

The provision of technical assistance and cooperation in countries facing outbreaks of severe communicable disease is a statutory function of WHO. A scheme for providing such assistance has been in operation by the Division of Communicable Diseases, since the establishment of WHO.

A panel of consultants, including experts in virology, who agree to be available at short notice has been designated by WHO. Members of the panel, together with WHO staff members, have provided critical assistance in recent years in several countries during outbreaks of poliomyelitis, yellow fever, Marburg, Lassa and Ebola haemorrhagic fevers, Crimean-Congo haemorrhagic fever, and Rift Valley fever. It is essential to the function of the panel that they may call on the resources provided by the Collaborating Centres for Reference and Research, including the availability of high security laboratories for identification of the highly pathogenic and contagious viruses. The scheme is operated in close collaboration with other Divisions of WHO, including the Division of Vector Biology and Control. WHO provides logistic support from Geneva and elsewhere.

The maintenance of this capability by WHO is regarded as a vital activity of the Organization. Member states should be strongly advised to set up early-warning systems to detect epidemics rapidly and to make provision for immediate dissemination of information on outbreaks. The experience acquired in emergencies should be shared with countries at risk by publications, scientific meetings and contributions of resources to field operations.

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