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The epidemiology of virus diseases

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The epidemiological occurrence of different virus diseases shows marked variations. These concern seasonal and geographical distribution as well as the occurrence of diseases in different ages, sexes and races. The word epidemiology means, literally translated from the Greek language, 'the knowledge of what is over the people'. The traditional meaning of epidemiology is the science dealing with the occurrence of infections and disease. Many viruses may cause both clinical and subclinical infections. Both of these are important in the spread of infections.

The term epidemic is arbitrarily defined to mean the occurrence of a particular disease in a frequency exceeding that which should be expected under normal conditions. When a disease shows instead a habitual presence within a more restricted area the term endemic disease is used. The term pandemic disease is used to denote an outbreak of infections of exceptional proportions, including a spread over continents.

Surveillance of the epidemiology of infectious diseases is important for many different reasons. The awareness of the development of an epidemic may have a number of consequences. Since general therapeutic measures for the control of virus diseases are not yet available, various preventive interventions have to be made. These may include isolation of infectious individuals, mechanical protection (gloves, coats etc), use of disinfectants to prevent the spread of virus and appropriate passive and active immunizations, when applicable. The introduction of different schemes for limited or general vaccination against different virus diseases has often had a dramatic influence on the occurrence of these diseases. It has become increasingly important to monitor these changes in the epidemiological occurrence of certain diseases by different methods of surveillance.

Methods of surveillance of the epidemiological occurrence of infectious diseases

Notification of communicable diseases

Various reporting systems can be developed. These may register the morbidity and mortality in a certain disease. This information can be expressed as prevalence – the number of cases occurring at a fixed time point; incidence – the number of new cases during a predetermined period of time; or frequency – the total number of ongoing cases in a given group during a specified period of time. These systems may vary from the most simple one, i.e. the counting of new cases (numerical system) to
a somewhat more informative one in which name and age of patients are also noted (nominative system). In more extensive information-notification systems further data of epidemiological value may be included, such as the suspected source and place of infection, data on the onset of disease, occurrence of other similar cases etc. All reporting systems have their weaknesses and have to be evaluated with great caution and by persons who are aware of the limitations. A low incidence may be due to a poor reporting system; conversely, an improvement of a reporting system may give a false impression of an increase in the number of cases.

Almost all countries in the world try to follow the epidemiological situation by different reporting systems. At the World Health Organization in Geneva reports from all over the world are compiled by a special viral disease unit. A special group is surveying the epidemiology of poliomyelities. In addition, special centres and working groups deal with specific viral diseases. Thus there exist two influenza virus centres, one in London (UK), and one in Atlanta (USA).

**Studies on the presence of immunity**

The distribution of a disease in a population can also be determined by measurements of immunity to the infectious agent in different age groups, so called seroepidemiology. A prerequisite for such studies is that suitable serological methods are used and that samples are collected from a representative fraction of the population. It is important that the serological technique used has a high sensitivity and that it gives reliable results.

In contrast to notification systems registering disease, the seroepidemiological approach allows the identification also of subclinical infections. As an example it can be mentioned that the true nature of poliomyelitis infections was not discovered until it was possible to determine the presence of serum antibodies. It then became evident that apart from poliomyelitis causing paralysis there was also a large number of subclinical infections. The disease was found to be most prevalent in countries where the infectious agent spread less readily and where naturally-induced immunity deriving from infections early in life was relatively low.

Another means of studying immunity to a certain disease is to use provocation tests. Attenuated virus strains are used as the agent of provocation. The response to or resistance against infection with such a virus can provide information on the absence or presence of immunity. Occasionally it is found that immunity is present even when no antibodies can be demonstrated. In these cases a state of sensitization exists and the body reacts on provocation with a booster reaction.

**Identification of virus**

In the beginning of an acute epidemic it is particularly important to identify the causative agent. Isolation and a detailed characterization of virus have a particular epidemiological importance, for example in the case of genetically labile viruses such as influenza virus and foot-and-mouth-disease virus. The possibility of confirming or excluding long-term carriers of virus, for example hepatitis B carriers, is also of epidemiological interest. The diagnostic possibilities of identifying virus at an early stage of the disease are now rapidly improving. This will improve the possibilities of introducing preventive measures and, in the future, of using antiviral drugs effectively.
The dissemination mechanisms of virus infections

In order to understand the mechanisms of the spread of infections three basic circumstances must be taken into consideration. These are the reservoir and source of infection, the transmission from this source, and the availability of susceptible hosts.

Reservoir and source of infection

Viruses may spread from many different sources and the contagiosity of the diseases they cause varies extensively. Most virus infections spread from man to man but animals or insects may also be a source of infection. The latter kind of infections are referred to as zoonoses. Concerning the spread of infections between humans is important to define whether it is dependent on an uninterrupted chain of contacts between acutely infected individuals or whether the virus may be continuously reintroduced into circulation from chronic infections or activated latent infections.

The contagiosity of an infection is dependent on (1) the amount of virus excreted, (2) the stability of the virus, (3) the duration of time of the excretion of virus and the relationship of this time to the possible occurrence of clinical symptoms, and (4) the route of exit of virus from infected individuals. It should be emphasized that healthy infected individuals are a relatively more important source of infection than diseased bed-ridden individuals and, further, that diseased individuals frequently spread large quantities of virus either before the appearance of overt symptoms or during the prodromal phase of disease. The incubation period for viral diseases varies from between a few days and many months. In these days of extensive international travelling it is a fact that within the incubation period of most viral diseases any part of our world may be reached. Consequently, a broader spectrum of viral diseases is now being encountered, in particular in industrialized countries. A broader assortment of available methods for the laboratory diagnosis of imported virus infections therefore is required in these countries.

Transmission of infection

Virus infections may be transmitted by a variety of different routes. The route of exit from the individual or animal which is the source of infection is of decisive importance. Respiratory infections may spread by aerosol. However, the importance of this route of transmission probably is overrated. Instead, spread of infected mucosal secretion from mouth-nose via hand (object) may play a dominating role. In special cases infected saliva may spread the infection in connection with kissing, for example, EBV in teenagers, or biting, for example rabies from a dog or other animal. Gastrointestinal infections spread from stool via hand or contaminated water. An example of the latter situation is hepatitis A; the virus may be excreted into sewage water for more than a week before the appearance of disease and this virus may accumulate in clams, for example, and spread via the ingestion of contaminated seafood. Swimming pools are another potential source of waterborne virus infections.

Virus may also exit from mucous membranes other than those in the respiratory and gastrointestinal tracts. Eye secretions may be infected and a spread of adenovirus infections from this source has been observed in connection with the use
of tonometers in ophthalmological clinics. That the urogenital tract may be an
important source of virus infections has become increasingly apparent only recently.
Urine may be contaminated with viruses, for example large quantities of CMV is
excreted by children with urogenital disease. However, the presence of viruses in
secretions or blood in the genital tract probably plays a much larger role than
virus-contaminated urine in the spread of infections. Sexual transmission can be a
vehicle for herpes simplex virus type 2, hepatitis B, CMV and other infections.
Transmission of virus via infected blood is seen in the case of hepatitis B and non-A
and non-B hepatitis from transfusions or contaminated needles and syringes and,
inevitably, in the wide spectrum of infections spread by vectors such as mosquitoes,
ticks, etc. Infected skin is the origin of the spread by contact for infections caused
by poxviruses, some herpesviruses (HSV, varicella) and papillomaviruses. A final
route of transmission to be mentioned is the vertical (transplacental) spread of virus
from a pregnant woman to the fetus.

Availability of susceptible hosts

The third prerequisite for the continued spread of infections is the availability of
susceptible hosts. Some virus infections induce an immunity of limited duration.
This pertains to certain local infections in the respiratory tract and probably also in
the gastroenteric tract. In this case repeated infections may occur. However, it is a
characteristic feature of most generalized virus infections that they induce a highly
efficient immunity which confers a lifelong protection against disease. Local
reinfections without symptoms may occur in the immune individuals, but these
limited infections probably do not represent a source of further spread of infection.
With epidemics of generalized virus disease, for example measles, there is an
accumulation of immune individuals. When a certain fraction of the population is
immune the further spread of an infection, which is dependent on a chain of
transmission between acutely infected individuals, is restrained. The percentage of
the population which needs to be immune to establish this herd immunity varies for
different viruses. In the case of a highly contagious virus like measles it has been
shown to exceed 90 per cent. The size of a population and the frequency of contact
between individuals also influence the possibilities for maintaining a continued, and
most of the time, low-grade, endemic spread of infections. It has been found that
under conditions prevailing in industrialized countries a population in excess of
300,000 is required to allow a continued circulation of measles virus. Thus in a
country like Iceland measles epidemics will 'burn out'. New epidemics will occur
provided that a sufficient number of non-immune individuals have accumulated
and the virus is reintroduced into the society from without.

The eradication of smallpox

Smallpox is an example of a disease caused by one type of virus. Infections with this
virus can be prevented by vaccination. There is no animal reservoir for smallpox
virus and the infection can only be transmitted by direct contact between acutely
diseased individuals. These were the conditions that set the stage for the global
eradication of smallpox which was achieved in 1977. In order to reach this goal it
was not found necessary to establish a herd immunity in populations in all
countries. Instead it was experienced that the chain of transmission of disease could
be effectively interrupted by vaccination of individuals in the surrounding areas of
the infected population, a technique referred to as containment measures.
Epidemiological patterns of virus infections

As already discussed, the fraction of immune individuals determines the epidemic vs. endemic occurrence of virus infections. This ratio fluctuates in the yearly occurrence of different infections and in some cases patterns of epidemic occurrence can be discerned. In non-immunized populations in industrialized countries, measles epidemics occur at 2–5 year intervals and each epidemic lasts for 3–4 months. The intervals between epidemics of, for example, mumps and rubella, are some years longer owing partly to the relatively lower degree of contagiosity of these infections.

Many virus infections also show characteristic patterns of seasonal occurrence. In temperate climates enterovirus infections occur during the late summer and autumn whereas respiratory infections like influenza are winter diseases (cf. Figure 21.3). Obviously the patterns of social life determining the intensity and form of contacts between individuals play a role in this contagion, but there must also be other important but as yet undefined factors.

Examples of the epidemiology of some virus diseases

Measles, mumps, rubella and varicella

The reservoir and source of infection of all these common childhood diseases is man alone. Only one serotype of each virus has been identified throughout the world. Both clinical and subclinical infections occur although the latter are rare in the case of measles. The immunity following disease is long-lasting – for practical purposes a life-long immunity. In temperate climates these diseases appear in waves at 5–10 year intervals. Figure 21.1 gives the annual number of cases of measles reported from district officers in Sweden. In this relatively sparsely populated country with a temperate climate, measles returned in waves with 4–7 year intervals before vaccination was introduced on a limited scale in 1972. In tropical countries both the patterns of seasonal and yearly appearance are different. Serological epidemiological studies (Figure 21.2) show that the other childhood diseases occur at somewhat higher ages than measles, in part a reflection
of their lower contagiosity. Furthermore the intervals between epidemics of mumps, rubella and varicella are somewhat longer than for measles.

In northern Europe most children have been infected with measles by the age of 12. The percentage of individuals immune to mumps and varicella is 80–90 per cent and to rubella only 40–50 per cent at this age. This is of importance since men contracting mumps during or after adolescence may develop orchitis which occasionally leads to infertility, and women contracting rubella during early pregnancy may transmit the infection to the fetus, which may cause fetal damage.

![Graph showing percentage of children presenting demonstrable antibodies to measles, mumps, and rubella in different age groups in Sweden before the introduction of vaccination.](image)

*Figure 21.2. Percentage of children presenting demonstrable antibodies to measles, mumps, and rubella in different age groups in Sweden before the introduction of vaccination.*

From the epidemiological point of view, varicella differs from the other three diseases in that it gives latent infections. When an endogenous infection with varicella virus is activated and causes a development of zoster, a spread of virus from skin vesicles may cause varicella in non-immune children in the surrounding area.

**Influenza**

Influenza virus is an example of a genetically labile virus. It can change its antigenic character abruptly and extensively – *antigenic shift*, at 10–20 year intervals, and also gradually from year to year – *antigenic drift*.

Influenza A appears in pandemics which occur after an antigenic shift. The antigenic composition of the virus has been so extensively altered that the immunity derived from earlier influenza virus infections no longer provides protection. In particular, the H (haemagglutinin) antigen is important for the immunity, but also the N (neuraminidase) antigen may play a role. The nomenclature used for classification of the different influenza virus variants include identification of the
serotype A, B or C, the place where the strain was first isolated and its H and N characters. The PR8 variant from the 1930s was named A/PR8/34 (H1N1). In the years 1947 to 1956 a variant with the H and N characters H1N1 prevailed. In 1957 a new extensive pandemic wave started, the ‘ Asiatic flu’ caused by influenza A/Asia/57 (H2N2), and in 1968 there was again an antigenic shift to influenza A/Hong Kong/68 (H3N2). The most likely explanation of the occurrence of antigenic shifts in influenza virus is a genetic reassortment in connection with a simultaneous infection of cells with a human and animal influenza A virus. For unknown reasons new strains appear primarily to originate from Asia. In 1978 the old strain from the 1940s, A(H1N1), unexpectedly returned. It remains to be explained how this strain had managed to survive in nature.

So far mainly people born after 1957 have become infected by this strain which illustrates that influenza virus infections induce a long-lasting immunity.

Between the shifts of H and occasionally also N antigens, antigenic drift causing minor changes in these virus surface components can be registered. Example of variants generated by drift are influenza A/England/72 and A/Texas/77 both of which derived consecutively from the A/Hong Kong/68 virus (Figure 21.3). The mechanism behind antigenic drift in influenza is mutational changes in the virus haemagglutinin and possibly also neuraminidase.

Other respiratory infections

The common cold is the most common of all viral diseases. It is caused by numerous different rhinoviruses and coronaviruses and many still unidentified
Examples of the epidemiology of some virus diseases

viruses (see Chapter 34). Many of these viruses probably induce a fairly shortlived local immunity. However, the great number of agents involved in this disease has hampered detailed epidemiological evaluations.

Other respiratory infections may give a more severe disease than coryza because of involvement of lower parts of the respiratory tract. The importance of different viruses varies partly at different ages. In the first years of life RS virus is an important cause of capillary bronchitis. The epidemiology of RS virus infections is unique because of the apparent absence of any transfer of immunity during the prenatal period.

**Enteric infections**

It is characteristic of enteric viruses that they are relatively resistant to heat and to many disinfectants, that they are excreted in large quantities in the stools, and that the course of the infection in many cases is subclinical.

Polio virus infections, which are the ones most thoroughly studied, may serve as an example of enterovirus epidemiology. Under poor hygienic conditions the virus circulates more or less constantly in the community and most individuals are infected during the first years of life. At this age many of the children are protected against viraemia by maternal antibodies. Other unknown, age-related mechanisms also seem to play a role in preventing a central nervous system involvement of the infection at this age. There is an increasing risk of contracting paralytic disease when a person is infected later in life. Thus the frequency of paralytic cases among subclinical cases is about 1:1000 to 1:10 000 when the infection occurs in the first years of life but may be as high as 1:10 when adults are infected.

Polio in an epidemic form started to emerge in countries with improving hygiene. The first epidemics involved children and were encountered around 1860 in Sweden. With improving hygiene the disease in Scandinavia gradually came to attack more teenagers and adults. Because of this epidemiological pattern, poliomyelitis is referred to as a *disease of civilization*.

In recent years it has been demonstrated that a broad spectrum of different viruses can cause enteric infections. Rotaviruses in particular have been disclosed as an important aetiopathological agent in infantile diarrhoea.

**Sexually transmitted virus diseases**

Herpes simplex virus (HSV) type 2 is the most extensively studied sexually transmitted virus disease. Both acute and activated latent infections may be the source of spread of virus. Serological epidemiology has shown that whereas HSV type 1 infections accumulate during the preadolescent years, infections with type 2 occur in connection with the establishment of sexual relationships. It has been noted that the availability of modern contraceptive techniques has increased the frequency of sexually transmitted diseases, including infections with HSV type 2. Other viruses also may be spread by sexual contacts but the relative importance of this route of transmission is poorly defined. Hepatitis B is discussed in this context and the possibility of this virus spreading has a special relevance because of its capacity to establish chronic infections. Chronic hepatitis B represents a particular problem in homosexual men.
Virus diseases transmitted from a pregnant woman to the fetus – (vertical transmission)

The *vertical transmission* is used when a virus is transmitted either during pregnancy to the fetus or to a child in connection with delivery. The most important cases of fetal damage caused by such a transmission are congenital rubella and CMV infections (see Chapter 15). From the epidemiological point of view it is of importance that children with these congenital diseases are excreting virus for periods of months to years after birth. The paradoxical effect - that a pregnancy causes a physiological immunosuppression which leads to activation of some latent infections - should also be mentioned. One example is activated CMV infections. This virus can be isolated from 4 per cent of pregnant women at the time of delivery. However, in terms of fetal damage, primary infections with CMV appear to play a major role.

Slow virus infections with non-immunogenic infectious agents

Certain very unusual epidemiological circumstances were revealed concerning the non-inflammatory and lethal infectious disease, kuru, which mainly afflicted women and children in a special area of New Guinea (see Chapter 17). It was revealed that the causative agent was likely to have been transmitted in connection with funeral rituals. The practising of these rituals ceased in 1957 and no person born after that year has developed the disease. However, cases of kuru still appear. The routes of natural transmission of Jakob-Creutzfeld disease, which is the equivalent of kuru in countries other than New Guinea, are unknown. Clusters of cases at various times and locations have been encountered, but the source of infection has not been detected. Certain cases of Jakob-Creutzfeld disease may be due to intrafamiliar spread. In a few cases transmission in connection with medical interventions has been identified.

Diseases spread by artificial inoculation

Diseases hitherto unrecognized in industrialized countries became noticeable when they were found to be spread by the increasing use of injection and transfusion techniques. Among these diseases hepatitis B has been studied most extensively (see Chapter 30). Also other as yet not well defined viruses (non-A – non-B hepatitis virus) are transmitted in a similar way giving rise to what has become known as nosocomial or iatrogenic infections (diseases spread in connection with medical treatments). Rigid measures with the particular aim of preventing the spread of infected blood have been successful in reducing the circulation of hepatitis B within hospitals.

Hepatitis of both B and non-A, non-B types can be transmitted outside hospitals especially by addicts using intravenously injected drugs and within family milieus.

In connection with organ transplantation virus may be carried over from the donor to the recipient. CMV has been found to be transferred commonly in this way in connection with both kidney and heart transplantation. Corneal transplantation has caused a transmission of Jakob–Creutzfeld disease in one case and rabies in a few cases. Jakob–Creutzfeld disease has been also transmitted to two individuals in connection with stereotactic electroencephalography.
Zoonoses

Certain virus diseases in man emanate from animal reservoirs. Like humans, the animals may show symptoms or be healthy carriers. One of the most dreaded zoonoses, rabies, is transmitted by direct inoculation by a bite of, for example, a dog, wolf or bat. Examples of indirect transmission are the disease nephropatia epidemica in Scandinavia and the closely related Korean haemorrhagic fever, which are transmitted by contact with material contaminated by virus-infected rodents.

However, the most common route of spreading of a zoonosis is transmission by a vector. At least 50 different haemorrhagic fevers have been categorized, mainly from tropical areas (see Chapter 26). Yellow fever is the most wellknown disease. In Europe tick-borne encephalitis of eastern and Scandinavian types are prevalent. The reservoirs are wild and domestic animals. Characteristics of this kind of disease are the endemcity and, in temperate climates, seasonal appearance. The epidemiology of these diseases is determined by a complex interaction between factors such as infected animals, environment, climate, season and immunity. From the epidemiological point of view zoonotic infections in man in most cases represent a blind alley, i.e. no further spread of infection to other individuals can occur. The only exception is second- and occasionally third-generation spread of Ebola–Marburg virus infections to relatives and hospital personnel from close contact with patients under primitive conditions. The risk of transfer to laboratory personnel in connection with analysis of samples from patients with these kinds of rare diseases, including Lassa fever, should be appreciated.

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