



## REVIEW

### VIRUS ZONOSSES — A LONG-TERM OVERVIEW

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#### INTRODUCTION

Zoonoses may be described as infectious diseases transmissible between vertebrate animals and man. As such, zoonoses are two-or-more host per one infectious agent systems, in which one of the hosts happens to be man. Zoonoses are thus interesting not only because of their relevance to human health, but because they are high-profile models for multi-host infectious diseases in general. From this perspective, it is also clear that the study of non-zoonotic, multi-host infections might lead to a better understanding of zoonoses, and the sources and evolution of human infectious disease in general.

Zoonoses have been classified in a number of ways, but largely on the basis of the routes and mechanisms of transmission between man and other animals [1–3]. However an alternative classification scheme is that shown in Table 1, in which zoonoses are classified according to their likely history. Although not water-tight, in that some zoonotic diseases cannot be placed neatly under just one heading, this scheme does provide a more useful framework for the discussion of questions such as "Where do infectious diseases come from?", and of the relationship between zoonoses and established human infections. Many generally accepted infectious diseases of man can thus be seen to have originated probably in the historically distant (but in evolutionary terms, fairly recent) past as zoonoses. What follows is a discussion of some of the concepts behind, and arising from, the scheme outlined in Table 1.

#### MEASLES — A HUMAN DISEASE OF PROBABLE ZONOTIC ORIGIN

Measles virus is extremely labile; it cannot survive in the environment for more than a few hours and so is reliant on relatively close contact between the infected host and a susceptible potential host for transmission. As measles is generally an acute infection, and infection provokes a strong, long-lasting immune response, maintenance in the population relies on there being a constantly available sufficient supply of susceptible hosts to which the virus can be transmitted during the relatively short period that hosts are infectious. Measles therefore simply cannot survive in human populations below a size sufficient to generate this supply — empirically approximately 300 000–500 000 [4].

This concept of a threshold population size of susceptible hosts can be expressed mathematically by considering a simple model infection [5, 6] in which

$$R_p = \beta SL$$

where  $R_p$  is the “replication rate” of the infection (essentially the number of new cases of infection generated by each existing infectious host),  $\beta$  is the “transmissibility” of the infection (and therefore compounds aspects of the inherent infectiousness of the pathogen and the contact behaviour of the host),  $S$  is the density of susceptible hosts and  $L$  is the “infectious period” (how long an infected host remains infectious). Thus, when  $R_p$  is greater than 1, the incidence of infection increases, whereas if  $R_p$  is less than one, the incidence decreases and the infection will eventually disappear from that population. Assuming  $\beta$  and  $L$  remain constant,  $R_p$  will increase as  $S$  increases, and it will only exceed 1 (and hence the infection will not tend to disappear from the population) when the population density of susceptibles exceeds a threshold ( $S_T$ ), given by:

$$S_T = \frac{1}{\beta L}$$

Archaeological evidence suggests that human populations did not reach the threshold density required for measles until around 6000 years ago, and certainly not until after the end of the last ice age. Measles and many other epidemic diseases of man must thus be relatively new. The simplest explanation is that they were, until recently, infections of non-human animals — in other words they were zoonoses.

These “diseases of civilisation” [7] might be compared to, for example, most human herpesvirus infections. Herpesviruses are generally extremely host-specific, genetically stable viruses which cause persistent infections. This long infectious period ( $L$ ) means that the threshold density is very low, so that infection may be present at almost any density of susceptible hosts. The human herpesviruses were therefore probably present in human populations much earlier than the epidemic viruses. These features of herpesvirus infections suggest that these viruses probably evolved with their hosts, rather than only recently jumping species.

Such arguments, of course, provoke the question, “What, then, were the animal origins of the measles virus?”. Measles virus is a morbillivirus, and as such is very closely related to both rinderpest virus of cattle and canine distemper virus (CDV). Because at the same time that human populations were attaining the sort of densities at which measles virus might have been able to circulate, humans were also domesticating cattle and dogs, some

Table 1. A classification scheme for zoonoses based on likely history

| Classification  | Likely history  |
|---|---|
| Human infectious diseases with an ancient zoonotic derivation | Epidemic/endemic human infections with a distant non-human source, e.g. measles   |
| Human infectious diseases of recent zoonotic derivation       | New or emerging human epidemic/endemic infections with a recent non-human source, e.g. HIV  |
| Established zoonoses  | Infectious diseases with a non-human reservoir host, which are occasionally transmitted to humans, e.g. rabies and cowpox viruses   |
| New and emerging zoonoses                                     | Infectious diseases with a non-human reservoir host which have only recently (been noticed to?) spread to man, e.g. hantaviruses  |
| Parazoonoses  | Infectious diseases endemic/epidemic in man, but which periodically change in virulence owing to a genetic input from non-human pathogens, e.g. antibiotic resistance transfer from animal to human bacteria, or genome reassortment (genetic shift) in influenza viruses |

workers have argued strongly that either rinderpest or, more likely, CDV is the ancestor of the measles virus [7]. CDV certainly has a wider potential host range than is often imagined, and may include man [8–10]. However, the true origins of the measles virus will almost certainly never be known, and the recent epidemics of previously unknown morbilliviruses in seals and other marine mammals [11], and particularly the recent morbillivirus epidemic in horses in Australia that also caused two human deaths [12], clearly demonstrate that there are, and probably always have been, more morbilliviruses in the seas and the earth than are dreamed of by even philosophical virologists.

#### HIV AS AN EXAMPLE OF A HUMAN INFECTION OF RECENT ZOOLOGICAL DERIVATION

There is little doubt that, whenever the first cases of human immunodeficiency virus (HIV) infection may have occurred, the present world-wide epidemic of HIV and AIDS is a new phenomenon. Despite recent challenges to the time-keeping of the HIV molecular clock [13], it is generally accepted that HIV-2, at least, originated between a few decades and a century or so ago in African monkeys [14], in which closely related lentiviruses circulate without causing very much, if any, disease. However, these viruses have probably occasionally been transmitted to man for centuries, and it is interesting to speculate as to why the HIV, and consequently AIDS, epidemics have only developed recently. One clue to part of the reason, at least, may be the observation that only very small changes in the value of  $R_p$ , for example from 0.9 to 1.1, will have dramatic consequences in terms of whether an infection disappears or spreads in a susceptible population. In the case of the HIVs, changes in economics and human behaviour (affecting both  $\beta$  and  $S$ ), such as the development of pan-African road systems and world-wide air travel, have undoubtedly contributed to their initial spread.

That HIV causes such severe disease in humans whereas most lentiviruses cause relatively little disease in their natural hosts probably reflects the relatively recent association of HIV with man. However, it should not be assumed that viruses inevitably evolve to become progressively less and less pathogenic in a host population. Rather, pursuing our simple model of infection, natural selection will favour virus strains with combinations of  $\beta$  and  $L$  giving values of  $R_p$  which are greater than those of their competitors, and such strains will thus come to dominate in a population.

#### MYXOMATOSIS — A MODEL OF AN EMERGING DISEASE

A well-documented example of how a pathogen might behave in a new host population was the introduction of the myxoma virus into susceptible European rabbit (*Oryctolagus cuniculus*) populations in both Europe and Australia. Immediately after introduction, when  $S$  was large, highly virulent strains of virus, which grew to high titres in rabbit tissues (high  $\beta$ ) but caused up to 100% mortality, were selectively advantaged. However,  $S$  decreased very rapidly, through both virus-induced death and acquired immunity, which decreased the frequency of contact between infectious and susceptible hosts. Strains causing longer infectious periods (increased  $L$ ) were therefore selected over more virulent strains. Note that  $L$  is inversely related to virulence, because in this instance virulence almost equates to virus-induced death rate ( $\alpha$ ), and  $1/\alpha = L + \text{incubation period}$ . Moreover, virulence is positively correlated with transmission rates ( $\beta$ ) insofar as  $\beta$  reflects virus titres in infectious hosts. Therefore as the circulating strains became less virulent

(increased  $L$ ) there was a decrease in  $\beta$ . Then, as more resistant rabbits were selected, more virulent strains became advantaged again, probably because of the associated increase in  $\beta$ . The relationship between the myxoma virus and wild rabbit populations now appears to be fairly stable — smaller populations of rabbits exist in dynamic equilibrium with moderately virulent viruses [15–17]. Mutations resulting in over-pathogenic virus strains tend to kill the host before adequate virus has been passed to other hosts (decreased  $L$ ). On the other hand, low virulence strains of virus are generally out-competed by the moderately virulent viruses already circulating, which grow to higher titres in rabbit tissues and cause more and larger lesions from which arthropod vectors can transmit virus (i.e. have higher values of  $\beta$ ). Selection pressure on the virus thus favours a combination of  $L$  and  $\beta$  which tends to maximize  $R_p$ .

It should be remembered that virulence is often only a by-product of a variety of virus properties, and thus is only one factor among many in determining the dynamics of an infection in a population. Selection for or against virulence will depend entirely on its relative contributions to  $\beta$  and  $L$  (which will vary according to both the virus and the host) and the relative contributions of  $\beta$  and  $L$  to  $R_p$ .

There is, however, one important complication to the argument that strains of virus with maximal  $R_p$  will be expected to dominate in a population which is particularly pertinent when the virus causes persistent infection of individuals, as is the case with HIV. Under these circumstances, strains of virus with the highest value of  $R_p$  *within* the individual host will also be selected for, and these strains may not be those with the highest  $R_p$  at the host population level. The value of  $R_p$  observed in the host population may therefore be less than it would otherwise be [18].

#### RABIES AND COWPOX AS EXAMPLES OF ESTABLISHED VIRUS ZOOSES

Rabies is a good example of a multi-host infection which has been studied for a long time [19], and of which one of the hosts is man. Caused by lyssaviruses, different species and biotypes circulate in different reservoir hosts in different parts of the world. In Europe the rabies virus is presently endemic in red foxes (*Vulpes vulpes*) [20], but is thought to have originated from a domestic dog strain of virus on the Russian–Polish border. After successive passage through wild foxes the present biotype is well adapted to foxes, which are  $10^5$  times more susceptible to it than are domestic dogs. The epidemiology of fox rabies in continental Europe has been studied in great detail with a view to developing better control programmes, and a simplified model (based on [21]) is shown in Fig. 1. Although simple, the model appears to reflect well the dynamics of the disease in the field. For example, computer simulations of the final equation,

$$dN/dt = aS - (b + qN)N - \alpha I$$

(where  $N$  is the total fox density,  $a$  is the birth rate,  $b + qN$  is the density-dependent death rate in uninfected foxes,  $\alpha$  is the death rate due to rabies, and  $I$  is the density of infectious foxes) using figures for virus and fox biology measured in the field, predict the approximately 3–5 year population cycles seen in real fox populations in which rabies is endemic.

This and later more sophisticated models also make interesting predictions about the relative efficacies of vaccination compared with culling for the control of fox rabies [22]. If rabies is to be controlled in Europe, then the effective density of susceptible foxes must

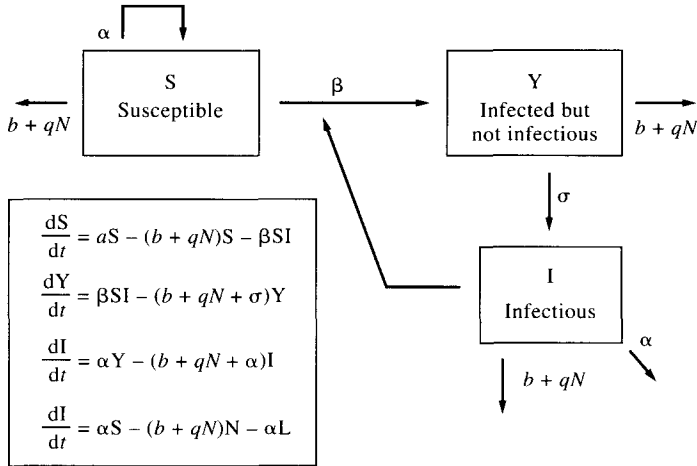


Fig. 1. Rabies in foxes. A flow diagram showing a simple model of the epidemiology of rabies in European red foxes (*Vulpes vulpes*) based on References [20] and [21]. Each box represents the density of foxes at a different stages of infection. *S* is the density of susceptibles; *Y* is the density of infected but not infectious foxes and *I* is the density of infected infectious foxes. The total density of foxes,  $N = S + Y + I$ . The densities of each subpopulation vary according to birth rate ( $a$ ), the natural, density-dependent death rate ( $b + qN$ ), the death rate due to rabies ( $\alpha$ ), the transmission rate ( $\beta$ ) and the rate at which disease (and infectiousness) develop ( $\sigma$ ). The first three equations in the box describe the rates of change in each subpopulation, e.g. in the second equation, the density of infected, but non-infectious, foxes (*Y*) is increased by infection of susceptibles (dependent on  $\beta$ , *S* and *I*) and is decreased by the natural death rate ( $b + qN$ ) and the rate of disease progression to infectiousness ( $\sigma$ ). The fourth equation is simply the sum of the first three, and demonstrates that the variation in the total fox population due to rabies should be predictable from knowing readily measurable parameters such as the normal birth ( $a$ ) and death ( $b + qN$ ) rates, the total fox density ( $N$ ), the proportion of susceptible (*S*) and infectious (*I*) foxes, and the rabies-specific death rate ( $\alpha$ ).

be reduced below the threshold ( $S_T$ ), which the models predict to be approximately 0.2–0.5 fox/km<sup>2</sup>. In Great Britain the density of fox populations varies enormously; the average rural fox density is about two foxes/km<sup>2</sup> but urban densities are often much higher. It can thus be seen that 75–90% of rural foxes would have to be either killed (not achievable in the long term) or vaccinated (just possible in some areas) to eradicate rabies in rural foxes should it cross the English Channel, whereas the necessary reduction by killing or vaccination of a higher proportion of the urban fox population (which seems less inclined to take vaccine-containing baits) would be very difficult.

Cowpox (caused by an *Orthopoxvirus*) is an occasional zoonosis, the epidemiology of which has recently undergone radical re-assessment. Although generally assumed to be endemic in cattle [23], most humans with cowpox have no history of contact with cattle, and bovine cowpox is actually very rare [24]. That cattle are unlikely to be the reservoir host of cowpox virus is to some extent predictable from the lack of reliable reports of virus isolation outside of Europe and Western Asia — unlike pseudocowpox virus (a *Parapoxvirus*) which has been exported with European cattle and is now found world-wide. Rather, the reservoir hosts appear to be wild rodents [24–26]. At the Eastern extreme of the geographical range of cowpox virus, in Turkmenia, the reservoir hosts are mainly souslicks and gerbils (*Rhombys opimus*, *Citellus fuleris* and *Meriones libyans*), whereas in

Western Europe the reservoir hosts appear to be voles (*Clethrionomys glareolus* and *Microtus agrestis*) and woodmice (*Apodemus sylvaticus*).

Interestingly, domestic cats are now the host in which cowpox is most frequently diagnosed in several European countries [27, 28] — and are also the source of over half the human cases seen in Great Britain [29]. Both feline and human infection have a marked autumnal incidence in Western Europe [27, 28], which probably reflects the increased population size and activity of wild rodents at that time of year, but the precise mechanisms of transmission from, and among, the reservoir hosts remain unknown, and are the subject of ongoing studies. The probable epidemiology of cowpox, in the bicentenary of Edward Jenner's first use of cowpox as a smallpox vaccine, is shown in Fig. 2.

Although only a rare pathogen of humans, a thorough understanding of the epidemiology and host range of the cowpox virus in wildlife is useful, for example, for assessment of any risks associated with the use of recombinant vaccinia-rabies vaccines in wildlife — in particular, assessment of the risk of hybridization with the vaccinia vector [30, 31]. Also, cowpox virus is not the only *Orthopoxvirus* with a wildlife reservoir. Monkeypox virus, for example, is endemic in squirrels (*Funisciurus* spp. and *Helioscirus* spp.) in West Africa, and furthermore, causes a disease in man clinically indistinguishable from smallpox [32]. Study of the epidemiology of the cowpox virus in European wildlife may therefore provide a readily accessible model for other, less easily studied, poxviruses, and indeed, the relationship between the epidemiology of endemic virus infections and the dynamics of their host populations in general.

#### HANTAVIRUS — A NEW/EMERGING ZONOSIS?

Hantaviruses are bunyaviruses of wild rodents, in which they cause no disease. Different strains of *Hantavirus* circulate in local species of rodent in different areas of the world, and although all the strains so far recorded appear to be infectious to man, their human pathogenicity varies enormously from strain to strain [33–35]. The type strain, Hantaan virus, for example, causes Korean haemorrhagic fever with renal syndrome (HFRS) in man with up to 20% mortality, whereas most strains from Western Europe and (until recently) North America, generally cause only sub-clinical infection or mild disease (nephropathia epidemica) with very low mortality. HFRS is an established zoonosis in parts of Asia and

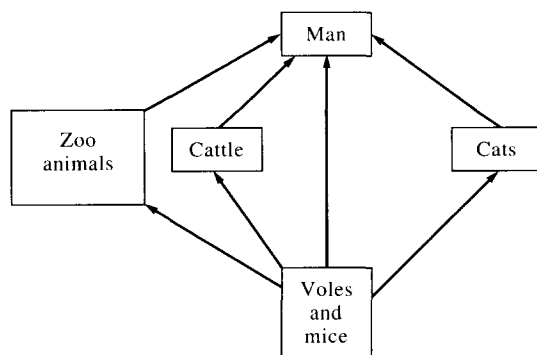


Fig. 2. The epidemiology of cowpox virus.

Eastern Europe and is often seen in agricultural workers during the harvest season, presumably when contact between humans and wild rodents is greatest.

Recently, however, newly recognized strains of virus have been isolated in North America, which can cause acute, severe respiratory disease (hantavirus pulmonary syndrome; HPS) with up to 60% mortality in man [36, 37]. HPS in North America is contracted through contact with infected wild mice, particularly pinion and deer mice (*Peromyscus* spp.), and the recent fairly large outbreaks appear to have followed unusual weather conditions which caused a population boom and the mice to come into closer contact with man than usual. Interestingly, it has been suggested that a recent increase in the incidence of human hantavirus infections in Europe was due to abnormally large populations of wild rodents [38]. Although retrospective studies have shown that cases of HPS occurred sporadically before the recent outbreaks, it seems reasonable to view it as a new zoonosis which has occurred in response to environmental changes and consequent alteration of the reservoir host's behaviour.

#### PARAZOONOSES — TRANSFER OF GENETIC MATERIAL FROM ANIMAL TO HUMAN INFECTIOUS AGENTS

In addition to those infections which are clearly zoonotic, in that the causative agent is transmitted from non-human animals to man, there are a number of mechanisms whereby animal pathogens (or, very often, non-pathogens) can contribute to the virulence of established human pathogens. A good example, in bacteria, is the transfer of antibiotic resistance on bacteriophages or plasmids. Among viruses, probably the best example, although it is still largely theoretical in its application, is genetic reassortment in influenza viruses. Good reviews of this are to be found elsewhere [39–41], and it will therefore be discussed only briefly here.

In essence, influenza viruses undergo antigenic change by two distinct mechanisms, antigenic drift and antigenic shift. Antigenic drift is caused by serial point mutations in the virus genome and is responsible for the continual slight changes in antigenicity which enable established human influenza viruses to cause minor epidemics in generally immune human populations each year. However, the antigenically novel strains of human influenza virus, which appear every few decades, probably arise through shuffling of the segmented genomes of existing human and animal strains of virus. The most likely scenario involves co-infection of swine with human strains (which do not generally infect birds) and avian strains (which do not generally infect humans), particularly in the Far East where large populations of humans, swine and wildfowl live in close proximity, and the consequent genetic reassortment of the two strains. This gives rise to strains of virus with markedly different antigenic (and perhaps other virulence) properties from those to which most people are immune. The consequent world-wide epidemics cause high mortality — for example the pandemic of so-called “Spanish ‘flu” in 1918–19 probably killed approximately 15–25 million people.

#### THE FUTURE

The arguments and examples discussed above make it clear that virus zoonoses have been, are, and probably always will be with us. New virus zoonoses emerge as humans increasingly enter new environments and change the environments in which they live. Some of these zoonoses may themselves become established in human populations — only small

changes in the behaviour of virus and/or host, affecting  $\beta$ ,  $L$  and/or  $S$ , may be needed to transform an occasional zoonosis ( $R_p \leq 1$  in man) into an established human infection ( $R_p \geq 1$ ). The realization of these threats, triggered particularly by the world-wide AIDS epidemic and HPS in North America, and given extra impetus by recent outbreaks of, for example, Ebola in Africa [42], has led to the development of a new (or rather has given new respectability to an old) field in infectious diseases, that of emerging infections. This now has its own journal (the *Journal of Emerging Infectious Disease*, available free on the World Wide Web at the URL <http://www.cdc.gov/>), international conferences and international monitoring and discussion groups (e.g. see the Promed archives at the URL [gopher://vetinfo.wustl.edu](mailto:gopher://vetinfo.wustl.edu)). However, without long-term, international political will, all this may come to nothing, and with the ever-increasing demands placed on the environment, human population growth and expanding international travel, that may have unfortunate consequences.

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