Animals, public health and the example of cowpox

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Summary
Public attitudes towards animals are often contradictory. In developed countries where the problem of food security has been solved to a large degree, public concern is concentrated on food safety and animal welfare, along with a debate on the social status of both domestic and wild animals. Zoonoses are often the focal point of these concerns. In developing countries (which often have the greatest biodiversity), wildlife constitutes an uncontrollable source of often unknown zoonoses.

The authors attempt to analyse the link between animals and public health. Special attention is given to the example of cowpox, a disease which has been recognised as a zoonosis for more than two centuries but the epidemiology of which has recently been rediscovered.

Keywords

Definition and introduction

According to the Dictionary of Veterinary Epidemiology, zoonoses are diseases or infections that can be transmitted naturally between humans and other vertebrate animals (52). Since the publication of the last edition of Zoonoses and Communicable Diseases Common to Man and Animals (1), zoonoses have often been at the forefront of public awareness, not least through the public debates on bovine spongiform encephalopathy, the so-called 'mad cow' crisis (46).

Public attitudes towards animals are often contradictory. In developed countries, where the problem of ensuring an adequate food supply (food security) has been largely solved, the emphasis is on food safety. However, concern for animal welfare is increasing and is accompanied by debates on the 'social status' of animals (38). These two ideals are not always compatible, for instance, concerns for animal welfare obviously favour the medical care of food-producing animals. However, the demands of consumers for safer food have led to the introduction of legislation to limit the maximum levels of drug residues allowed in animal products such as meat, eggs and milk. Predictably, this legislation has led to a reduction in the range of medicinal products available for the treatment of food-producing animals (36). A further obvious contradiction exists between the demand for increased production efficiency (demands expressed by the consumer in the form of powerful economic lobbying), and the desire for improved welfare of intensively farmed animals (29), expressed largely through politico-societal debate (47).

In developing countries, food security is far from being attained, and an increase in production of animals for food is still the priority. The next food revolution in these countries is likely to include an increase in consumer demand for meat and other animal products (21). In addition, large animals are required not only for food but also for fibres and draught. These predicted changes raise concerns over sustainability, environmental protection and the maintenance of biodiversity in developing countries. Domestic animals can be an important source of environmental degradation and often compete with wildlife for resources (23, 26, 48). Moreover, wildlife remains an important source of food for humans in many developing (and developed) countries. All these factors contribute to the biodiversity crisis, even though wildlife is partly protected as an important source of income through tourism.
The interaction between wildlife and domestic animals is further complicated by the inter-specific transmission of infections, many of which are zoonotic (41). As illustrated throughout this volume, wildlife is the reservoir of numerous infections that affect domestic animals and/or man, and an important potential source of new and emerging zoonotic diseases. Changes in the relationships between man, livestock and wildlife, disruption of ecosystems and the expansion of international trade, all contribute to the emergence of new diseases. In summary, the maintenance of biodiversity will always be associated with the maintenance of reservoirs for potential zoonoses.

Other changing aspects of zoonoses are social and scientific (50). The globalisation and the increasing speed of information transfer have introduced a bias to the perceived relative importance of zoonoses. Without the use of new diagnostic methods and epidemiological approaches, many 'new' infections might have remained unnoticed. Understanding of the epidemiology of many zoonoses has also improved with the introduction of a more ecological approach. The example of cowpox, described later in this paper, illustrates this point well. For nearly two centuries this infection was thought to originate from cattle (42), and only recently has the biology of this infection been understood more fully.

Research that provides a better understanding of the underlying biology of zoonoses will enable a more rational approach to the control of these diseases, while taking into account the need for poverty alleviation in developing countries, sustainability, biodiversity (39) and animal welfare (3, 22). However, it is also apparent that approaches to control will vary significantly according to the local geographical, social and cultural environment.

Animal agriculture and global change

In the first two decades of the 21st Century, the global structure of animal agriculture is likely to undergo drastic changes. Fuelled by population growth, rising per capita income and urbanisation, demand for meat and milk in the developing world is expected to rise by 2.8% and 3.3% per year, respectively (21). According to the International Model for Policy Analysis of Agricultural Commodities and Trade (IMPACT) of the International Food Policy Research Institute, the share of developing countries in total world meat consumption will expand from 47% currently, to 63% by 2020. Per capita consumption of meat and milk in the developing world is projected to be only 29 kg meat and 63 kg milk in 2020, which represents only one third to a quarter of the current consumption level in the industrialised world. At these moderate levels of consumption, meat and milk will fulfil a critical role in providing essential (micro)nutrients of high bio-availability, especially to vulnerable groups, such as young children and pregnant women.

In parallel with this scenario of global change, the local uses of livestock are also evolving. Especially in Asia, Africa and Latin America, food-production is assuming a more important function for livestock and the traditional, non-food functions such as draught, manure and asset-creation are diminishing in importance. At the same time, important shifts are occurring in global trade. Global trade in meat and milk is increasing, driven by international and regional trade agreements combined with lower transport costs. Moreover, there is an increasing recognition that rural growth cannot be adequately sustained by domestic consumption only, but requires export, even for the least developed countries. For the livestock sector, this requires increasing attention to food quality and food safety standards, to meet the demands of the consumer and livestock industries in the importing country.

Within this changing environment, the role of all stakeholders in the sector needs to be redefined, especially that of intergovernmental organisations such as the Office International des Epizooties (OIE).

The above trends require that more attention be paid to the international public-good aspects of animal agriculture, including the following:

a) food security, with greater attention to policies and technologies that increase the efficient use of scarce input resources

b) the environmental aspects of animal agriculture, with particular focus on technologies and policies that enhance the positive and mitigate the negative effects of livestock on the environment

c) the social aspects of animal agriculture, and particularly the technologies which benefit the rural and urban poor, and for which the incentives for private sector development are inadequate

d) the food safety aspects of animal agriculture, especially policies, institutions and technologies that enable a growing participation of the developing world in international trade

e) the animal welfare aspects of agriculture, and economically viable means of increasing welfare

f) disease control and eradication programmes, which will enable animals to move freely between countries.

Thus, a world-wide challenge exists, namely: how to accommodate all the contradictory aspects of animal production and human-animal bonds so as to alleviate poverty in a sustainable manner and minimise the risk of zoonoses, while maintaining biodiversity, ensuring safe global trade and travel and increasing the efficiency of animal food production in developing countries.
Public health and the need for new paradigms in animal health

Animal health is entering a new era. In developed countries, the emphasis on food security and endemic animal disease has been replaced by concerns over the economic consequences of overproduction. This has given rise to a switch in emphasis to food safety and increased concerns over the combined effects on the environment of intensification and abandonment of land traditionally used in more extensive agricultural systems. The countryside (the relic of biodiversity in much of western Europe), has traditionally been maintained by agricultural systems; if these are abandoned, other ways of maintaining the countryside must be found. Meanwhile, in developing countries, there is still a substantial deficit in both production and consumption, but due to the globalisation of trade and the trend towards urbanisation, there is also an increasing need for much greater food safety to protect both human and animal health. The recent outbreaks of African swine fever in West Africa (although this is not a zoonosis), exemplify how infectious diseases of animals can ruin a local animal industry and consequently severely disrupt the human food supply. An example of a risk of zoonosis associated with the combination of international trade and local production systems is that of influenza. In Asia, the relationship between certain types of farming systems and the emergence of new influenza viruses able to infect humans has been clearly demonstrated (2); pigs act as a 'mixing vessel' for avian and human strains of influenza virus, from which antigenically new strains of pathogenic virus emerge (43).

As already suggested, maintaining biodiversity often involves maintaining the reservoirs of diseases of livestock and humans. Furthermore, infectious agents such as viruses may undergo rapid co-evolution in new hosts (24), and in the same way that small changes in the ecosystem may lead to the emergence of a new zoonosis, such zoonoses can themselves be the evolutionary origin of endemic disease in humans.

In this global context, international organisations such as the OIE also need to evolve in order to fulfil new roles in infectious disease control in the arenas of both animal and human health.

Expectations of consumers in developed countries

As outlined above, in developed countries, the demands of consumers are largely aimed not at food security but at food safety. This has many consequences for animal health, not least that the restrictions placed on the use of medicinal products in food-producing animals will have detrimental effects on animal health and welfare, and therefore possibly on human health (55). This negative impact may be partly overcome by the increased use of vaccines or genetic resistance (through selection or, more controversially, genetic modification), since many of the principal health problems of food-producing animals have infectious or parasitic origins (40). However, as illustrated elsewhere in this volume, the main public health problems associated with animals are still of biological origin, and are not caused by residues of veterinary medicinal products. Thus, as a general rule, the better animal health is protected, the better humans are protected. In developing countries where food supply remains a problem for the majority of the population, the role of public organisations remains the provision of an adequate food supply and appropriate health measures.

Maintaining biodiversity

There is global consensus on the need to maintain biodiversity, but inevitably, this will also maintain the reservoirs of infections that can spread to domestic animals or humans. Interactions between domestic animals and wildlife that involve disease transmission are diverse (41). Numerous infectious agents may be exchanged, including viral, bacterial and parasitic diseases. Furthermore, the economic, geographical and ecological situations that permit reciprocal transmission are themselves extremely variable, as is the degree of intensification of animal production, whether in domestic or wild species. The extent of surveillance and diagnostic activities is also variable.

The problem is complicated further because some wild species are bred in captivity under ranching or farming conditions. Examples can be cited in industrialised countries (such as the deer industry in Scotland) and in countries of Africa such as Zimbabwe. Some wild species may even be introduced into a country for subsequent release or maintenance in captivity (for example, ostriches and crocodilians), and this can create further difficulties for international trade. In addition to considering the risks posed by wildlife for domestic animals or people, it is also necessary to consider domestic species and humans as sources of risk to wildlife. One of the most striking examples of this is the spread of rinderpest through Africa at the end of the 19th Century, with often dramatic extensions to wildlife (37, 45).

Cowpox: an infection of wildlife transmissible to domestic animals and humans

The adoption of a more ecological approach to the study of infectious diseases has introduced new concepts to the understanding of the biology of infections, including zoonoses (18). Although cowpox is not one of the principal diseases of either domestic animals or humans, it provides a
useful example of how such approaches can challenge the way a disease is regarded. Cowpox provides an interesting model for studying the interactions between host and infection dynamics in natural, wildlife, host populations, and also for examining variations in virus pathogenicity in different hosts.

Cowpox virus is a member of the genus Orthopoxvirus within the family Poxviridae, and as such is closely related to smallpox virus (now nearly eradicated) and vaccinia virus (the modern smallpox vaccine, the origin of which is unknown). Cowpox virus is found only in Europe and neighbouring regions of western Asia. The virus has a wide host range, but circulates mainly in wild rodents (Fig. 1). Despite the name of the virus, cattle are rarely infected, and domestic cats are the species in which clinical disease is most often diagnosed. Human infection, although rare, is more commonly reported than bovine infection, and can often be traced to contact with an infected cat, or sometimes direct contact with rodents. In addition, infection is sometimes reported in other 'accidental' hosts, including dogs and various mammals kept in zoos.

In Great Britain, the dynamics of cowpox virus infection have been studied in great detail in wild populations of bank voles and wood mice (8, 9, 17, 28). In general, cowpox dynamics appear to reflect the population dynamics of each of the two hosts (Fig. 2). Bank vole and wood mouse populations in Great Britain undergo seasonal annual cycles, but not the multi-annual cycles seen in some rodent populations of Fennoscandia. Bank vole populations typically peak in early summer, and fall drastically in the autumn, while wood mouse populations peak later in the year and reach a low the following spring. Incidence of infection in both populations (as measured by seroconversion) appears to follow closely the host population cycle, and fits a model whereby infection rates at any time can be predicted by the number of susceptible and infected animals in the population the previous month (8, 9). Interestingly, further analysis of the field data suggests that little transmission may occur between the two species, despite sharing the same habitat (9). Furthermore, in contrast to the conventional assumptions, transmission in wild populations fits 'frequency-dependent' models better than those based on 'density-dependent' transmission. Thus, transmission probably relies on social

Viruses isolated at different geographic locations can vary considerably. Thus, cowpox virus isolates from Great Britain, although distinguishable by restriction enzyme analysis, are generally similar to each other and readily distinguishable from isolates found in central Europe or Asia, by molecular and biological assays. The largest variation in strains appears to be in central Europe, suggesting that modern cowpox virus may have originated in this area. This suggestion is supported by the theory that populations of small rodents lived in central Europe during the Ice Age and subsequently extended throughout Europe (13). A recent history of co-evolution and maintenance of the virus in bank voles, with occasional transmission to, and subsequent maintenance in, other species such as wood mice, would also explain several features of the modern geographic distribution of cowpox virus. For example, neither cowpox nor the bank vole have been reported in the southern half of Italy or most of the Iberian Peninsula. Wood mice, but not voles, are native to Ireland, and a survey of wood mice from Northern Ireland revealed no cowpox antibody. Indeed, until recently cowpox had never been reported in Ireland (Jenner mentioned the absence of the disease from Ireland in his inquiry of 1798) (31). However, several feline cases have recently been diagnosed in the Republic of Ireland (M. Bennett, unpublished findings), and an examination of the links between these cases and the expanding population of bank voles introduced into south-western Ireland approximately 100 years ago may yield interesting results.

**Fig. 1**
The host range and probable epidemiology of cowpox virus

**Infection in wildlife**
The species of rodent in which cowpox virus circulates probably varies according to geographical location; in many cases the species is not known. In western Europe, bank voles (Clethrionomys glareolus), field voles (Microtus agrestis) and wood mice (Apodemus sylvaticus) are the main reservoir hosts (17, 19). In northern Europe, virus has been isolated from root voles (Microtus oeconomus) (32), and in Turkmenistan, antibody has been detected in 15% of suslikcs (Spermophilus citellus), and 18% of giant gerbils (Rhombomys opimus), with virus isolated from 3 of 1,275 rodents tested (34). Antibody thought to reflect cowpox has also been detected in 9% of gerbils (Meriones libycus) and 2% of rats (Rattus norvegicus) in Georgia (54). However, rats in Great Britain did not have antibody to cowpox (56), and rats are unlikely to be reservoir hosts. If this was the case, the virus would be found world-wide. A similar argument applies to cattle, in other words, if cattle were the main host of cowpox, then the virus should be found, like pseudocowpox virus, wherever European cattle are present. Orthopoxvirus antibody and polymerase chain reaction (PCR) products have also been described in lemmings (Lemmus lemmus) and shrews (Sorex spp.) in Norway (53).

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Seroconversion occurs principally in juvenile and adult animals in wild populations of both bank voles and wood mice. A trend towards a higher prevalence in males than females has been reported among bank voles (28). There is no obvious sex bias in incidence. As in experimental infections, no obvious clinical signs of infection are observed. However, it is not yet known whether the reduction in fecundity described in experimentally infected bank voles and wood mice is also seen in naturally infected animals in wild populations (25). The experimental studies suggested that cowpox could reduce the annual fecundity of both wood mice and bank voles by perhaps 25% or more, through a delay in the production of a first litter. Such an effect, if seen in the wild, would be difficult to detect (since obvious signs of disease and mortality are absent), but could significantly influence host population dynamics.

Experimental infection of voles and wood mice with a strain of cowpox virus from Great Britain shows that all are susceptible to infection with small doses of virus by oronasal or skin inoculation, but that infection causes little disease (except a primary skin lesion with high doses of virus) (12; M. Bennett, unpublished findings). However, experimental infection of suslics and gerbils with a virus strain from Turkmenistan caused acute disease with 30%-100% mortality (34). Furthermore, while little virus was re-isolated from the voles and wood mice (although it can be readily detected by PCR (M. Bennett, unpublished findings), virus was routinely re-isolated in various tissues from the suslics and gerbils. In both cases, infection could be detected for more than four weeks in at least some animals.

### Infection in cats

The domestic cat is the species in which cowpox is most frequently diagnosed in western Europe, and unlike the natural rodent host, cats generally develop systemic disease (11, 14). Cats probably become infected by direct contact with infected wild rodents. The usual route of infection is through a break in the skin, often by contamination of a pre-existing wound or, perhaps, a fresh bite wound, although oronasal infection is also possible. Most infected cats are adults which inhabit rural areas and are known by their owners to hunt wild rodents. Furthermore, most cases are seen in the autumn (Fig. 3), reflecting the population and infection dynamics of rodents (Fig. 2). Although cat-to-cat transmission can occur, this is rare and seldom leads to clinical disease in the second cat. Thus, cats are not endemic hosts, and serological surveys generally detect only a low prevalence of infection.

In both natural and experimental feline infection, a primary skin lesion develops at the site of inoculation within a few days. A viraemia develops, mediated by white cells, probably monocytes/macrophages, with virus replication in lymphoid tissue, the lungs and turbinates (10). The viraemic phase
human cowpox, evidence suggests that this has not occurred. A virus (HIV) infection might lead to a rise in incidence of immunosuppression caused by human immunodeficiency. The precise incidence of human cowpox is not known, but is probably very low. Only one or two cases are reported annually in Great Britain, and serological surveys show a prevalence of only 0.7% (4). Although other areas of skin can be artificially infected, natural bovine cowpox is usually limited to lesions on the teats of dairy cows. This probably reflects areas of skin most likely to be both damaged and to come into contact with rodent-contaminated material. In contrast to the disease in cats, cowpox virus does not appear to cause systemic disease or more widespread skin lesions in cattle; the lesions are limited to the sites of virus entry. When bovine cowpox does occur, the disease can spread rapidly through the herd, probably on milking equipment (27).

Infection in other mammals

Cowpox, or orthopoxvirus antibody thought to be caused by cowpox, has also been reported in several other species. Two cases of infection in domestic dogs have been reported (14, 49). Several studies have detected a low prevalence of low titre antibodies in foxes (Vulpes vulpes), although others failed to detect antibodies (16, 30, 35). Foxes were found to be susceptible to experimental infection only with very high doses of a strain of cowpox virus from Great Britain (15, 16).

Interestingly, a related orthopoxvirus, ectromelia virus, has been isolated from farmed foxes (33). Although generally assumed to be a virus of mice (causing severe epidemics in laboratory mice), ectromelia virus has not been detected in wild house mice, and the true host of the virus is not known. A wild rodent reservoir may exist, particularly in eastern and central Europe, from which transmission to other species (such as foxes) can occur. Severe, often fatal, cowpox has been described in elephant, rhinoceros, ant-eater and okapi in various zoos in Europe (44), but the most frequently infected group of zoo animals has been felids. Two outbreaks, each involving several cheetahs, have been reported from zoos in Great Britain (5), and an outbreak affected lions and other species at the Moscow Zoo (34). The source of infection in the zoos in Great Britain was not determined, but the outbreak in the zoo in Moscow appeared to be due to infection in captive rats used to feed the cats. Isolated cases have also been reported in servals, lynx and ocelots kept in zoos. Infection in felids kept in zoos seems more severe than in domestic cats.
(pneumonia is particularly common in cheetah) and the mortality rate is high. Fortunately, however, infection is uncommon; an ongoing serological survey of cats in zoos in Great Britain has found no antibody in over 100 cats tested (M. Bennett, unpublished findings).

**Pathogenesis and epidemiology**

The clinical signs of cowpox in different hosts provide a good example of the way that a single virus (and a single set of ‘virulence’ genes) can cause very different diseases in different hosts, and may provide a model for studying the nature and evolution of virulence. In the natural reservoir hosts, with which the virus probably co-evolved, cowpox virus causes little disease. One hypothesis is that greater virulence in voles and wood mice might reduce transmission or prevent maintenance of the virus in wild populations. In this light, the effect of infection on fecundity in experimentally infected voles and wood mice is interesting, and further work is needed to determine whether this is a specific effect of virus infection or simply a measurable reflection of more general malaise, and to investigate whether transmission is affected. Certainly, the disease seen in some ‘accidental’ hosts, and caused by a wealth of well-characterised virulence genes, is not seen in voles and wood mice, and this suggests that such disease is not the normal product of the virulence genes. This underlines the importance of studying virulence in natural hosts, as far as possible, in the natural environment, if the true roles of virulence genes and the selection processes which determine their evolution are to be understood.

**Conclusions**

Zoonoses have developed an increasingly high profile in recent years, in the popular as well as scientific press. These diseases constitute a real challenge to the already difficult act of balancing intensification, globalisation of trade, increased livestock production and the provision of global food security against the need for sustainable agricultural practices, the maintenance of biodiversity and animal welfare. Greater consideration should be given to zoonoses when developing new farming practices, and particularly to the risks of new and emerging infections. In particular, the apparently contradictory desires for food security, food safety and animal welfare must be acknowledged, as well as the intimate, intricate, and sometimes dangerous, relationship between man, domestic animals and wildlife. In this context, the role of international organisations, such as the OIE, may be crucial in assessing and managing the risk posed by zoonotic diseases.

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### Animaux, santé publique et l'exemple de la variole bovine

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**Résumé**

L’opinion publique est souvent partagée à l’égard des animaux. Dans les pays développés, où le problème de la sécurité alimentaire a été, dans une large mesure, résolu, le public est surtout attentif à l’innocuité des denrées alimentaires, au bien-être animal et au débat concernant le statut des animaux domestiques et sauvages au sein de la société. Le problème des zoonoses se trouve souvent au cœur de ces préoccupations. Dans les pays en développement (qui présentent fréquemment la plus grande biodiversité), les animaux sauvages constituent une source incontrôlable de zoonoses souvent inconnues. Les auteurs étudient la relation entre les animaux et la santé publique. Ils examinent, notamment, le cas de la variole bovine, zoonose reconnue depuis plus de deux siècles, mais dont l’épidémiologie a fait récemment l’objet de nouvelles découvertes.

**Mots-clés**

Animales, salud pública y el ejemplo de la viruela bovina

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Resumen
La actitud del gran público respecto a los animales resulta a menudo contradictoria. En los países industrializados, que tienen en gran medida resuelto el problema del abastecimiento de alimentos, las preocupaciones de la opinión pública se centran sobre todo en la inocuidad de los alimentos y el bienestar de los animales, paralelamente a un debate acerca del lugar que corresponde en la sociedad a los animales domésticos y salvajes. La cuestión de las zoonosis suele hallarse en el centro de todas esas preocupaciones. En los países en desarrollo (que albergan casi siempre el mayor nivel de biodiversidad), la fauna selvática constituye una fuente incontrolable de zoonosis desconocidas. Los autores intentan analizar el vínculo existente entre animales y salud pública, haciendo especial hincapié en el ejemplo de la viruela bovina, cuya epidemiología se ha redescubierto recientemente pose a tratarse de una enfermedad reconocida como zoonosis desde hace más de dos siglos.

Palabras clave

References


