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Chapter 24

Public Health and Rodents: A Game of Cat and Mouse

Bastiaan G. Meerburg

Abstract Rodents are the most abundant order of living mammals, distributed on every continent except Antarctic and represent 43% of all mammalian species. Beside causing food losses and infrastructural damage, rodents can harbour pathogens that may cause serious problems to human and animal health. Unfortunately, rodent-associated problems are not an issue of the past as some may have thought, even not in the developed world. This chapter describes four factors that determine the risk and severity of human infection by zoonotic pathogens of rodents: human behaviour, human health condition, rodent ecology & behaviour and pathogen ecology & persistence. It provides an overview of these factors, their interrelation and also some directions for further research. Main conclusion of this chapter is that although science has come a long way already and we have won some small victories over the rodents, the game of cat (i.e. humans) and mouse is far from being settled.

The order of *Rodentia* is the most abundant and diversified order of living mammals and represents in total about 43% of all mammalian species (Wilson and Reeder 1993; Huchon et al. 2002). Rodents are distributed on every continent except Antarctica and include many of the most abundant mammals. For many centuries, opportunistic rodent species have been considered as serious pests because of the damage they cause to crops, stored produce or infrastructure and the role they play in the transmission of pathogens to humans and livestock. Improved public sanitation conditions like safe drinking water, the introduction of sewers and the development of efficient anticoagulant rodenticides in the 1950s resulted in an improved public health situation and created the illusion that rodent-associated problems in the developed world had become an issue of the past.

More recently, however, the concern about rodents in both the developing and developed world has grown again because of various reasons. These reasons are the following:

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- The distribution and abundance of various rodent species may be significantly affected by changes in land use (e.g. reforestation projects, urbanization);
- Climatic change may improve living conditions for certain rodent populations;
- Growing outdoor leisure activities increase the exposure of humans to rodents and their excrements and hence the transmission risk of rodent-borne pathogens;
- In some countries the government has receded from rodent control and put it out to contract to private companies. This has led to a serious lack of insight in the spreading and abundance of rodent populations, which is important to monitor the potential introduction and spread of rodent-borne pathogens;
- The human world population is growing rapidly and thus more food is needed. Rodents are responsible for huge pre- and postharvest losses (Meerburg et al. 2009b; Htwe et al. 2012);
- Environmental concerns, toxicological safety regulations and budget reductions have diminished rodent surveillance and rodenticide-based control in many countries;
- The increasing extent of resistance of rodents against second-generation rodenticides has reduced the efficacy and flexibility of rodent control (Pelz 2007; Buckle et al. 2013; Endepols et al. 2012);
- Rodents still play an important role in spreading (re-)emerging zoonotic diseases (Meerburg et al. 2009a).

Rodent presence can have serious implications for public health and be potentially hazardous as they amplify pathogens from their environment by forming reservoirs of zoonotic disease (Webster and Macdonald 1995; Gratz 1994). With reservoirs it is meant that rodents can harbour disease-causing organisms and thus serve as potential sources of disease outbreaks, but always via a vector (tick, sand-fly etc.). Besides as reservoirs, rodents can also act as carriers, which means that rodents that show no or limited disease symptoms but harbour the disease-causing agent, are capable of passing it directly onto humans (Meerburg et al. 2009a).

Two main transmission routes of pathogens can be distinguished (Meerburg et al. 2009a): the direct route (when rodents are carriers) or the indirect route (when rodents function as reservoir and transmit a pathogen through means of a vector), see Fig. 24.1. In the latter, this vector is often an arthropod, but can also occasionally be other animals, such as livestock. Rodents that are (either by accident or on purpose) ingested by livestock can transfer pathogens. When food originating from this livestock is not thoroughly cooked, this may lead to human morbidity (Meerburg et al. 2004).

If we now look at the risks and severity that are imposed by rodents to human health, there are several factors that are of importance (Fig. 24.2).

The first one is human behaviour. People with frequent outdoor leisure activities or which fulfil specific occupations (e.g. in the military, animal trapping or forestry) or those that live in degraded environments will be more exposed to rodent-borne zoonoses than others (Clement et al. 1997; Muliæ and Ropac 2002; Hukic et al. 2010, Sauvage et al. 2007; Bonnefoy et al. 2008). Exposure is the key word here, thus, for example also people that keep rodents as pets may experience higher risks

Fig. 24.1 The two main transmission routes, the direct route (*left*) and the indirect route (*right*). (Reproduced from Meerburg et al. 2009a)

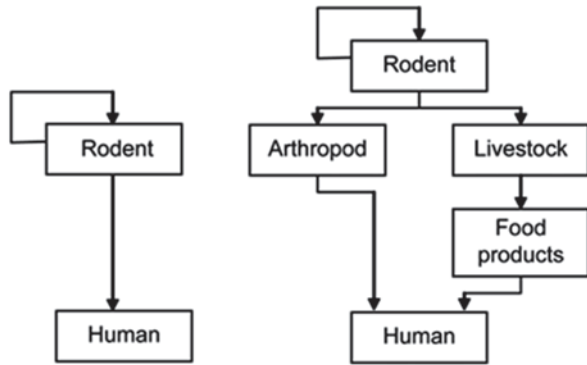
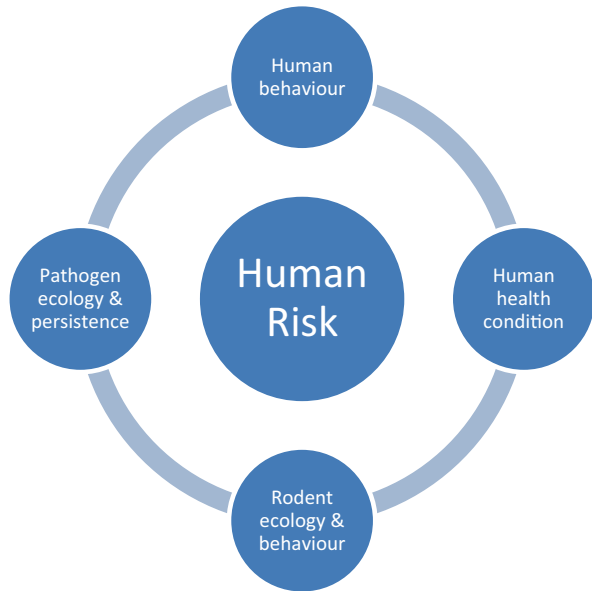


Fig. 24.2 Four factors determine the risk and severity of human infections by zoonotic pathogens of rodents: human behaviour, human health condition, rodent ecology & behaviour and pathogen ecology & persistence



of zoonotic infection. The risk of keeping pet rodents will be discussed more in detail later in this chapter.

The second factor is the human health condition. Generally, zoonoses pose unique transmission and disease risks if people are not in good health, such as immunocompromised persons, neonates, the elderly or pregnant women (Mani and Maguire 2009; Hemsworth and Pizer 2006) or may effect persons in specific age groups. As an example *Streptobacillus moniliformis* may be mentioned, the primary cause of rat bite fever in North America. Children under 12 years of age are mainly infected, and demonstrate an acute syndrome of fever, rash, and polyarthritis. Some years ago, a fatal case-report was reported, a 14-month-old-boy, who was exposed

to filthy living conditions and whose family had pet ferrets. Presumably, the boy was bitten by rodents as autopsy revealed a possible bite mark (Banerjee et al. 2011).

Also aspects such as vaccination coverage may influence the factor human health condition. From a number of studies, it is known that wild rodents can be reservoirs for orthopoxviruses (Tryland et al. 1998, Kinnunen et al. 2011). More recently, pet rats were discovered as a new potential source of local outbreaks with cowpox. However, smallpox-vaccinated patients tend to develop less severe reactions and heal more quickly (Vogel et al. 2012). Thus, there is a direct link between actions of public health services (vaccination) and the recovery rate (severity of infection) of infected persons.

A third factor of importance is rodent ecology and behaviour. As mentioned in the introduction, rodent ecology may differ over the years, depending on climatic factors, feed abundance and predation (Witmer and Proulx 2010). During a study in Namibia, mice entered buildings during the post-harvest stage, which may represent a period of food shortage for these mice in the field (Monadjem et al. 2011). If these species are coincidentally contracted with zoonotic pathogens, this may increase the risk of human infection. In a study from Cambodia, it was demonstrated that the rainy season is favourable for transmission of leptospires in rodents, particularly in rain-fed fields (Ivanova et al. 2012). Here, the human risk of contracting *Leptospira* spp. is determined strongly by the ecology of the rodents: in rice-fields, forest, secondary forests and their interface with agricultural fields the potential of humans for contracting leptospirosis infection is the highest (Ivanova et al. 2012).

But the link between rodent ecology and human health risks is not depending solely on one rodent species. Also the presence of other non-reservoir rodent species is important. In a recent study from Panama it was demonstrated that hantavirus prevalence in wild reservoir (rodent) populations and reservoir population density increased when small-mammal species diversity was reduced (Suzán et al. 2009). These authors thus claim that high biodiversity is important to reduce transmission of zoonotic pathogens among wildlife hosts (Suzán et al. 2009). Also host relationships form part of the rodent ecology and there can be significant differences in such relations within the same rodent species. In a study where host-tick relationships of the yellow-necked mouse (*Apodemus flavicollis*), a critical host in the maintenance of the zoonotic disease tick-borne encephalitis, were investigated it was demonstrated that the transmission potential was not evenly distributed among the yellow-necked mice population. The authors found that 20% of hosts most infested with ticks were accountable for 80% of the transmission potential, and that these hosts were identified as the sexually mature males of high body mass (Perkins et al. 2003). This leads to the impression that control efforts targeted at this host group would reduce the transmission potential significantly.

In the past, seasons of exceptionally high rainfall were thought to increase rodent populations (because plant growth would lead to abundant seeds and insects) and thus outbreaks of some rodent-borne diseases (Engelthaler et al. 1997; Brown and Ernest 2002). However, we now start to discover that such relationships between rodent population dynamics and precipitation are complex and non-linear. This was also the main conclusion after some scientists studied the El Niño phenomenon in

deserts of southwestern North-America (Brown and Ernest 2002). In agricultural contexts it is also difficult to predict exactly the breeding ecology of species. A recent study from the Philippines compared two rodent species *R. argentiventer* and *R. tanezumi* during four cropping seasons (two dry and two wet). The expectation was that *R. tanezumi* breeding would occur throughout the season, whereas the breeding of *R. argentiventer* would be strongly cued to the generative stage of rice crops (Htwe et al. 2012). However, it was found that their breeding ecology was exactly similar, with the onset of the breeding season at the tillering stage of the rice crops. The conception of adult females was highest during booting and ripening of the rice and the highest litter size occurred at booting and ripening of the rice (Htwe et al. 2012). Such information is essential in order to optimize the management of rodents in order to reduce harvest losses and pathogen transmission risks.

The fourth factor is pathogen ecology and persistence. Many of the mechanisms that mediate pathogen ecology and persistence only start being uncovered. Concerning hantaviruses in rodents, several host factors, including sex steroids, glucocorticoids, and genetic factors, are reported to alter host susceptibility and may contribute to the persistence of hantaviruses in rodents (Easterbrook and Klein 2008). Moreover, because of the recent discovery of structural and non-structural proteins in humans that suppress type I interferon responses, it is now thought that immune responses of rodent hosts could be mediated directly by this virus (Easterbrook and Klein 2008). In laboratory rats it was observed that *Leptospira interrogans* serovar Copenhageni initially disseminates extensively throughout the host, prior to clearance from all tissues except the kidneys, suggesting that the kidneys are immune privileged sites and that this is not caused by tissue tropism (Athanzio et al. 2008). In a study in black rats (*Rattus rattus*) in Madagascar, an important difference in plague resistance between rat populations from the plague focus (central highlands) and those from the plague-free zone (low altitude area) was confirmed to be widespread (Tollenaere et al. 2010). Moreover, these authors discovered that sex influenced plague susceptibility, with males slightly more resistant than females (Tollenaere et al. 2010). It is difficult whether this phenomenon is caused by rodent ecology, pathogen ecology or a combination of both. This is also the case with other findings. In Belgium, a close association between the distribution of hantavirus-infected bank voles and wet habitat types was found (Verhagen et al. 1986). In another, more recent, study from this country, a direct relation between climate and the incidence of human cases of nephropathia epidemica (NE) due to Puumala virus (PUUV) infection was found. High summer and autumn temperatures, 2 years and 1 year respectively before NE occurrence, relate to high NE incidence (Tersago et al. 2009). In the United States, human cases of Hantavirus Pulmonary Syndrome (HPS) were clustered seasonally and temporally by biome type and geographic location. In this study, exposure sites were most frequently found in pinyon-juniper woodlands, grasslands, and Great Basin desert scrub lands, at elevations of 1,800 m to 2,500 m (Engelthaler et al. 1997). This might be caused by presence of rodent reservoir hosts in these areas, but perhaps also because of favourable environmental conditions for pathogen survival. Pathogens do not only persist in the host itself, but may also survive for longer periods of time throughout the environment. For

example, *Yersinia pestis* biotype *Orientalis* remains viable and fully virulent after 40 weeks in the soil and is then able to continue its role in plague epidemiology (Ayyadurai et al. 2008). Moreover, if factors such as pH, viscosity and salt concentration are optimal, *Leptospira* spp. are thought to be able to survive in fresh water under low-nutrient conditions for over 100 days (Trueba et al. 2004).

It is clear that for eradication strategies more work has to be done on the pathogenesis of the various zoonotic pathogens which can be transferred by rodents. Especially the further development of genetic tools could lead to a better understanding of the virulence and survival mechanisms that are used by pathogens to ensure their persistence in different ecological niches and host reservoirs.

Often, there is a relation between the different factors and complex relationships between pathogen prevalence and rodent density appear likely. In North-Western Europe the main disease-causing hantavirus species is the Puumala virus (PUUV). The reservoir species for PUUV is the bank vole (*Myodes glareolus*), which exists in specific habitats. The risk for PUUV transfer from the bank vole to the human population via excretion of the virus in the environment is dependent on a myriad of biotic and abiotic risk factors, either rodent-, virus- or human-related, that vary in time and space. In a study from Finland, the effect of PUUV infection on the winter survival of bank voles was investigated (Kallio et al. 2007). These authors demonstrate that PUUV infected bank voles had a significantly lower overwinter survival probability than antibody negative bank voles. Thus, the pathogen is able to influence the host population dynamics. During a study on the ecology and demographics of hantavirus infections in rodent populations in the Walker River Basin of Nevada and California, it was found that antibody prevalence could vary within repeatedly sampled sites from 0 to 50% over the course of several months (Boone et al. 1998). In Tanzania, an African rodent (*Mastomys natalensis*) is thought to be the principal source of human infections with *Leptospira* spp. In a study where the dynamics of infection were modelled and in which the climatic conditions in central Tanzania were included, a strong seasonality was visualised in the force of infection on humans with a peak in the abundance of infectious mice between January and April in agricultural environments (Holt et al. 2006). In urban environments, however, dynamics were predicted to be more stable and the period of high numbers of infectious animals runs from February to July (Holt et al. 2006). In countries in Northern-Europe (Germany, Denmark) there are also regional differences visible in the level of encountered *Leptospira* spp. infected-rats (Runge et al. 2013, Krøjgaard et al. 2009). Why these differences occur, is not yet fully understood.

As mentioned before, the risk of transmitting zoonotic pathogens to humans is largest if the exposure risk is maximal. Handlers and owners of pet rodents are often in direct contact with them and may experience significant risks. Some years ago, there was an outbreak of 28 cases of multidrug-resistant *S. enterica* Serotype Typhimurium in the United States. After the outbreak, 22 patients were interviewed. Of them, 13 (59%) had had contact with rodents purchased from retail pet stores (Swanson et al. 2007), while 2 patients (9%) acquired salmonellosis through secondary transmission from a primary patient who had been exposed to rodents. Moreover, 7 patients (32%) had no identified rodent exposure. Matching isolates

were obtained from one submitted urine specimen and 27 stool specimens from patients (Swanson et al. 2007). These authors warn that consumers and animal workers should be aware that rodents can shed salmonellae and should expect rodent excrements to be potentially infectious. Thus, handling of pet rodents may result in health risks, especially for children. When handling pet rodents, their cages or bedding, the hands should be thoroughly rinsed with water and soap. Animal vendors should be aware if substantial diarrhoea-associated complications or death occurs among rodents intended for sale (Swanson et al. 2007).

Some years earlier, an human infection with Lymphocytic Choriomeningitis Virus (LCMV) in the United States was found by the CDC to be associated with pet rodents (hamsters and guinea pigs). Here, the risks extended also beyond the owners of these pets. In this particular case, LCMV was responsible for the death of 3 immunocompromised persons (organ transplant recipients) who received these organs from pet rodent owners (Anonymous 2005). More recently, workers at a rodent breeding facility in the United States were confronted with a LCMV infection. In total, 52 current and former employees of the facility were tested, and 13 of them (25%) demonstrated a recent LCMV infection (Anonymous 2012).

Exotic rodents may introduce pathogens that were previously unknown to continents. For example, in 2003 a monkeypox outbreak in pet distribution facilities in the US occurred after import of infected African prairie dogs (Anonymous 2003). In total, monkeypox was confirmed in 35 persons, of which none died, but the outbreak required vaccination of 30 persons with smallpox vaccine.

Commercially-traded wild prairie dogs were also responsible for an outbreak caused by *Francisella tularensis* type B in Texas. Antibodies to this pathogen were found in one person that was exposed, thus leading to the first evidence of tularemia transmission from prairie dog to human (Avashia et al. 2002). Problematic was that in the period June-July 2002, more than 1000 prairie dogs were distributed from the facility where the pathogen emerged, to locations in 10 other U.S. states and 7 other countries (Avashia et al. 2002). These had to be traced back and were all euthanized. However, this case underlines the health risks to humans who handle wild-caught animals and underscores the speed of transportation of exotic species and their pathogens over the globe (Avashia et al. 2002).

A human cowpox virus infection is an uncommon and potentially fatal skin disease, which is confined to major parts of Europe. Patients may sporadically contract the pathogen by contact with infected cows, cats or small rodents. However, recently there is also a report from Germany (Munich), where 8 patients were infected by pet rats they had purchased at a local supplier (Vogel et al. 2012). Thus, pet rats can be considered as a novel potential source of local outbreaks of human cowpox virus infections.

Also, dermatophytes can be transferred to humans by rodents. In Switzerland for example, 9 isolates of the fast-growing dermatophyte species *Arthroderma benhamiae* were isolated from 8 children and 1 adult. Eight of the 9 patients had had previous contact with rodents, mostly with guinea pigs (Fumeaux et al. 2004). In another study, where the frequency and types of dermatophytes among both Guinea pigs and rabbits were determined (Kraemer et al. 2012), *Trichophyton mentagrophytes*

was determined to be the most common dermatophyte in pet Guinea pigs and rabbits, but asymptomatic carriers were regularly observed only in Guinea pigs. Consequently, pet guinea pigs carrying dermatophytes can be considered as a serious zoonotic risk for their owners, especially children (Kraemer et al. 2013).

An Australian patient who experienced an infection with *Streptobacillus moniliformis*, the causative agent of rat-bite fever, obtained this pathogen not because she was bitten by rats, but because she had had contact with her pets, including cuddling and kissing them (Papanicolas et al. 2012). This is a risk as *S. moniliformis* forms part of the commensal flora of the rat's oropharynx (Elliott 2007).

But not only handling or keeping pet rodents can impose a risk. Also commensal rodent species (species that live in or around a house or a farm) may lead to health risks. The risk of bites by rats inflicted in urban environments (often in substandard dwellings) and the spread of infection to humans is substantial. In the United States, there are hundreds of rat bite reports each year, while the number may even be underreported by a factor of at least ten (Bonney et al. 2008; Hirschhorn and Hodge 1999). Next to rat bites, ectoparasites that are associated with these rodents can spread additional infectious organisms. The rodents are sometimes also carrying endoparasites or other pathogens which may contaminate the local environment. A literature review on helminths in rodents in South East Asia showed that the highest helminth species richness was found in *Rattus tanezumi*, *Rattus norvegicus* and *Rattus argentiventer*, which are found in more human-dominated habitats such as agricultural areas or human settlements (Chaisiri et al. 2010). In a study in Tokyo, Japan, 17% of the brown rats (*Rattus norvegicus*) from urban areas carried leptospires in their kidneys and cases in human patients could directly be linked to these rats via DNA-analysis (Koizumi et al. 2009). Moreover, rodents in agro-ecological surroundings can be infected with *Salmonella* spp. and *Campylobacter* spp. and transfer these bacteria to livestock or amplify their number in the farm environment (Meerburg and Kijlstra 2007). In this way, a resident infected rodent population could lead to continuously returning infections in the farm environment, with all the negative consequences for both livestock and farmers. The exact risk dimension of livestock-pathogen-human-wildlife interactions is not yet known for many pathogens. Two pathogens may serve as an example here: *Coxiella burnetii*, the causative agent of Q-fever, and Hepatitis E virus (HEV). Concerning *Coxiella burnetii*, it has been implicated in many studies that rodents function as reservoirs for Q-fever, but their exact role in pathogen maintenance, geographic spread and transmission still remains to be clarified (Meerburg and Reusken 2011; Webster et al. 1995). Problematic in determining the exact contribution of rodents is that basic wildlife and domestic cycles of *C. burnetii* infection can operate independently, but will overlap in many instances as many areas in the world are occupied by both domestic and wild animals (Meerburg and Reusken 2011), which makes it hard to unravel their exact contribution. In a recent study from Japan (Kanai et al. 2012) in which wild *Rattus norvegicus* were caught near a pig farm where HEV was present, it was demonstrated that in these rodents there was a relatively high prevalence (17.9%). Consequently, these authors conclude that *R. norvegicus* may be a carrier of swine

HEV in endemic regions, but that the HEV contamination risk due to rats in human habitats remains unclear (Kanai et al. 2012).

Consequently, there remains much work for scientists to be done. Concerning the factor human behaviour, the use of Geographical Information System (GIS) technology could prove to be a useful tool for the identification of endemic foci and high-risk areas for numerous pathogens that are transmitted by rodents. Such technology was recently tested in a study in Cyprus (Psaroulaki et al. 2010), where rats were used as disease sentinels and tested for seropositivity on six microbial agents. By optimizing this technology, more information could be acquired about possible outbreak areas, which facilitates informing the general public by public health officials.

When considering the factor human health condition, one should remember that the world population will increase the coming decades and also that the average age of the world population will increase. Thus, the number of people that may experience significant health effects when infected by zoonoses is growing. We do not yet know the exact dimension of the problem, but it is something to keep in mind.

High resolution remote-sensing could also prove useful to monitor the factor rodent ecology and behaviour. This was recently done in Kazakhstan, where great gerbil burrow systems were observed by means of satellite images (Addink et al. 2010). The occupancy rate of these burrows is a strong indicator for the probability of a plague outbreak. By monitoring the density of great gerbil burrow systems, or locating new or expanding foci, a direct contribution could be made to surveillance and control efforts (Addink et al. 2010). Of course, with such techniques it is not possible to monitor the ecology and behaviour of all rodent species. To gain more insight into the population dynamics and habitat preferences of rodents, field studies will remain necessary. By collection of small mammals in several habitat types, an action which was recently undertaken in Albania (Rogozi et al. 2012), one can gain more knowledge of the reservoir ecology in a country, and thus acquire more possibilities for reliable risk assessments for rodent-borne diseases. Moreover, also rodent identification via molecular methods, e.g. molecular barcoding using short genetic markers (Galan et al. 2012) may be useful as this will lead to a quicker and more accurate species identification. The previous will also prove its worth, if rodent dynamics and ecology will change in the future because of climatic change.

Concerning the factors pathogen ecology and persistence, there are also new opportunities. Fecal samples of wild rodents that were collected in California and Virginia were surveyed in order to obtain an initial unbiased measure of the viral diversity in the enteric tract (Phan et al. 2011). Viral RNA and DNA were randomly amplified. Phylogenetic analyses of full and partial viral genomes revealed many previously uncharacterized viral species, genera, and families, and close genetic similarities between some rodent and human viruses even reflected past zoonoses (Phan et al. 2011). In another recent study, a comparative approach was used to study microparasite species richness across rodent species according to the latitude where they occur (Bordes et al. 2011). The results demonstrated that virus species richness increased towards tropical latitudes, and that rodent litter size seemed to decrease when microparasite species richness increased independently from the

latitude. The authors thus claim that rodent species in the tropics harbour higher parasite species loads effectively, at least in terms of species richness for viruses, and that parasite species richness influences rodent life-history traits (Bordes et al. 2011). This information is also important for reliable risk assessments.

Finally, we may conclude that humankind has come a long way. We increased our knowledge and understanding and have gained some small victories over the rodents. However, there is no definitive victory over them yet, and although they are not able to defeat the cats (in this case the humans), they do still pretty well in avoiding capture. Let's hope that further scientific progress will lead to a better understanding about rodents and their risk for public health and that the contest between cat and mouse may end in a favourable way for humankind.

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