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FELASA recommendations for the health monitoring of mouse, rat, hamster, guinea pig and rabbit colonies in breeding and experimental units

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Abstract

The microbiological quality of experimental animals can critically influence animal welfare and the validity and reproducibility of research data. It is therefore important for breeding and experimental facilities to establish a laboratory animal health monitoring (HM) programme as an integrated part of any quality assurance system. FELASA has published recommendations for the HM of rodent and rabbit colonies in breeding and experimental units (Nicklas et al. Laboratory Animals, 2002), with the intention of harmonizing HM programmes. As stated in the preamble, these recommendations need to be adapted periodically to meet current developments in laboratory animal medicine. Accordingly, previous recommendations have been revised and shall be replaced by the present recommendations. These recommendations are aimed at all breeders and users of laboratory mice, rats, Syrian hamsters, guinea pigs and rabbits as well as diagnostic laboratories. They describe essential aspects of HM, such as the choice of agents, selection of animals and tissues for testing, frequency of sampling, commonly used test methods, interpretation of results and HM reporting. Compared with previous recommendations, more emphasis is put on the role of a person with sufficient understanding of the principles of HM, opportunistic agents, the use of sentinel animals (particularly under conditions of cage-level containment) and the interpretation and reporting of HM results. Relevant agents, testing frequencies and literature references are updated. Supplementary information on specific agents and the number of animals to be monitored and an example of a HM programme description is provided online (see http://lan.sagepub.com/suppl/DC1).

Keywords

health monitoring, rodents, rabbit, infections, sampling

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Environmental and genetic factors and their interactions may influence the suitability of an animal for use in research.[1,2] The occurrence of infectious agents in breeding or experimental laboratory animal facilities highlights the need to consider the animals' microbiological quality since it directly influences welfare, experimental variability and scientific research projects.[3] The use of animals of known biological characteristics is important in ensuring reproducibility of experimental results. The main objective of these recommendations is to harmonize health monitoring (HM) programmes (i.e. designing, sampling, monitoring, reporting and interpreting) which will help to improve knowledge about the microbiological quality of animals used in research and to meet scientific, legal, and welfare requirements.

Several groups of microorganisms are responsible for infections in rodents and rabbits. Most infections do not lead to overt clinical signs. Therefore, an absence of disease symptoms has only limited diagnostic value. Latent or inapparent infections, however, can have a considerable impact on the outcome of animal experiments. There are numerous examples of the influence of microorganisms on the physiology of a laboratory animal (behaviour, growth rate, relative organ weight, immune response).[1,4] Infections, apparent or inapparent, may confound scientific results, increase biological and experimental variability, and cause an increase in animal use. Contamination of biological materials such as transplantable tumours and other tissues, cell lines and sera or embryos and gametes[5,6] can occur as a result of latent infections in animals. Such contamination may in turn infect new animals or interfere with the materials' use. Some infections in laboratory animals can also infect humans (zoonoses).[7] For all these reasons, it is important that each institution establishes a laboratory animal HM programme as an integrated part of any quality assurance system. The cost of preventive measures and HM may seem high, but is low in relation to the total cost of the research project. Institutional HM programmes and testing laboratories can be accredited according to the Federation of European Laboratory Animal Science Associations (FELASA) guidelines for the accreditation of HM programmes and testing laboratories.[8]

It is important that animals are free of agents that may interfere with specific models or projects. However, it is also important to emphasize that it is not a requirement of these recommendations that all animals used in biomedical research are free from all of the microorganisms tested.

HM is a complex issue. Therefore, it is strongly recommended that a person with sufficient understanding of the principles of HM (preferably of FELASA Category D or equivalent) be identified as the individual responsible for devising and maintaining an HM policy for the facility. The use of these recommendations will be facilitated by basic knowledge of microbiology and of infectious agents of laboratory rodents and rabbits. Moreover, the success of a health management programme requires that all individuals who work directly (e.g. animal care staff, technicians, researchers) or indirectly (e.g. supply teams) with the animals should also have an understanding of the rationale of health management and monitoring. Efficient health management requires a culture of communication between all involved in the animal care and use programme, so that health screenings are properly performed, their results are correctly interpreted and subsequent actions are appropriate.[9]

The results of HM are summarized in a health report that is in a standardized format for clarity and ease of use. However it is important to emphasize that these reports are only a part of the HM programme, which also includes microbiological unit definition, sampling, sample analysis, results reporting and interpretation of the reported results.

The FELASA HM recommendations are aimed at all breeders (commercial and non-commercial) and users of laboratory animals (e.g. animal facility managers, veterinarians, scientists using animals for experimental purposes) as well as diagnostic laboratories. They provide a framework for HM of laboratory rodents and rabbits in breeding and experimental colonies, with the intention of harmonizing systems principally among countries associated with FELASA. The present recommendations represent a revision of previous FELASA recommendations for the HM of breeding and experimental colonies of rodents and rabbits[10] and shall replace them. Compared with previous recommendations, more emphasis is put on the role of a person with sufficient understanding of the principles of HM, opportunistic agents, the use of sentinel animals (particularly under conditions of cage-level containment) and the interpretation and reporting of HM results. Relevant agents, testing frequencies and literature references are updated. Supplementary information on specific agents and the number of animals to be monitored and an example of an HM programme description is provided online (see http://lan.rsmjournals.com/lookup/suppl/doi:10.1177/0023677213516312/-/DC1). These recommendations will be periodically reviewed and amendments published as necessary.

General considerations in the design of an HM programme

The present recommendations constitute a common approach for the HM of laboratory rodents and rabbits and the reporting of results. Relatively uncommon

species in current scientific use, such as Chinese hamsters and Mongolian gerbils, will not be addressed because there is not enough published information on infectious agents in these animals to make valid recommendations. Recommendations should be adapted to individual and local needs, research objectives, local prevalence of specific agents, the existence of national monitoring schemes, and other regulations such as those related to the production of sera and vaccines. However, microbiological status standards must be clearly defined and appropriate systems of preventive measures developed to meet those standards. A documented HM programme established in each animal housing facility should determine if the preventive measures have been effective and the microbiology quality goals have been met.

Animal facilities are structured into and organized as microbiological 'units'. A microbiological unit is defined as a self-contained microbiological entity, with separate space and traffic for animals, personnel and materials. The person responsible for the design of the HM programme defines the units and HM schemes tailored to the use of the unit. Therefore, different monitoring programmes may be necessary in the same facility. Table 1 gives examples of microbiological units.

The definition of the microbiological unit is a critical step in the design of the HM programme since it will influence the sampling programme, the nature and frequency of the tests, as well as the interpretation of the results. For example, since the risk factors and consequences of a microbiological contamination can be different in breeding versus experimental units, the design of the HM programme should reflect this diversity.

In a breeding facility, only a small number of people should have access. On rare occasions animals may be introduced, but only after following strict measures to safeguard microbiological quality. Given the possible wide distribution of animals from breeding facilities, the frequency and thoroughness of the monitoring programme is essential to prevent the spread of infectious agents to experimental facilities.

Table 1. Examples of microbiological units.

- A barrier facility (with one or more rooms) within which personnel, equipment and animals move freely or where animals are kept in open cages.
- An isolator.
- A group of microisolation cages where there are direct animal contacts allowing for horizontal transmission.
- A single cage (e.g. an individually ventilated cage handled in a laminar flow cabinet following strict hygienic measures).

In an experimental facility, both breeding and experimentation may occur. Introduction of animals from outside sources is usually necessary. In addition to animal care staff, numerous researchers enter the experimental animal unit to conduct protocols. Biological materials have to be introduced into an experimental animal unit and these may also need to be monitored.

The use of cage-level containment housing such as individually ventilated cages (IVCs) is now common in laboratory rodent facilities. Transmission of fomites or animal-borne infectious material between cages is dependent on the husbandry and handling procedures but is generally reduced compared with open cages. IVC housing has the potential to reduce the spread of both infectious agents and allergens. Under these conditions, HM has become a challenging task and strategies for proper sampling need to be developed for breeding and experimental populations independent of statistical considerations used in the previous recommendations.

Emerging infectious agents and new HM technologies are also a consideration. A new agent or technique does not change the goal of an HM programme, only the reporting or the means of monitoring. If the HM programme indicates the presence of an agent which, although not listed in these recommendations, is suspected of being important, this agent should be mentioned in subsequent reports and treated as other listed agents.

The HM programme must allow for the accurate assessment of the protective measures put in place in the unit. The design of the programme must be tailored to local needs and requires consideration of the microbiological unit(s), the animal species, the immune status and number of animals in the unit(s), the frequency of monitoring, which animals and sample(s) are to be collected, the organisms for which to test, the detection methods and the health history of the unit. In microbiological units containing more than one animal species, each species must be screened separately. Furthermore, susceptibility to infection and serological response may vary according to both age and differences in genetic background. Animals of varying ages should be selected for monitoring. If varied strains or stocks are present, as many as possible or even all may need to be screened, or the sampling should be rotated between strains and/or stocks over time, since the results will represent all animals of the same species within the same unit.

The thoroughness of an HM programme should reflect the level of risk that applies to a particular unit and the risk that it poses to other units (Table 2). Frequency of monitoring is also determined by both the biological characteristics and prevalence of

Table 2. Some factors that determine the risk of introducing unwanted agents into an animal unit.

Higher risk:
- Frequent introduction of animals (e.g. $>1\times$ per month).
- Units of varying microbiological status with close proximity.
- Introduction of animals from different breeding colonies (from one or several breeders).
- Movement of animals out of the unit for manipulation and subsequent return.
- Access of insects, wild or feral rodents to animal rooms or feed and bedding storage.
- Frequent introduction of biological materials originating from the same animal species that are housed in the unit.
- Multipurpose facilities with various kinds of experiments.
- Frequent entry of research personnel into the unit (in addition to animal care staff).
- Frequent turnover of animal care personnel working in the unit.
- Shared equipment that cannot be easily disinfected (e.g. imaging, behavioural).

Lower risk:
- Closed breeding colonies.
- 'All in–all out' system.
- Occasional introduction of animals.
- One or few types of experiments.

infectious agents. Highly infectious agents with a high prevalence should be tested for frequently. Monitoring frequency may also reflect the potential effect of an agent on a research programme underway. The current recommended minimum test frequencies are shown in Tables 3–7.

Choice of agents

The selection of agents to be monitored is determined by numerous factors including effects on animal health, effects on biomedical research (e.g. the confounding of scientific experiments as a result of physiological modulation), species specificity, zoonotic potential, prevalence, host factors (particularly immune status), desired unit microbiological status and historical results. Detection of an organism does not necessarily mean that it has to be eliminated.

The examples below show that the list of microorganisms monitored is neither exhaustive nor permanent. The list will change over time; infectious agents will rise and fall in importance. The current recommended agents to be monitored in each animal species addressed in this working group report are given in Tables 3–7. Monitoring for additional agents may be useful under specific circumstances: if they are associated with lesions or clinical signs of disease, if there is evidence of physiological perturbation or alteration in breeding performance, or when using immunodeficient animals. Limited information about agents and their effects on research can be found in Appendix 1 (see http://lan.rsmjournals.com/lookup/suppl/doi:10.1177/0023677213516312/-/DC1) and in various review articles and textbooks.[2,4,11,12]

Species specificity and zoonoses

Some microorganisms are host-specific or have a relatively limited host range, whereas other agents may infect various animal species. In addition, some of the microorganisms that may be present in laboratory animals can infect humans or vice versa (zoonoses).[7] Although the contemporary prevalence of potential zoonotic agents with few exceptions (e.g. *Staphylococcus aureus*) is rather low in laboratory rodents and rabbits, the potential risks necessitate continued surveillance for such organisms.[13] The risk of a zoonosis also exists when biological material is used. For example, there are reports of contamination of hamster tumour cell lines with lymphocytic choriomeningitis virus (LCMV).[5] Today, humanized immunodeficient animals are being used for studies of the human immune system, xenotransplantation and as infection models. These animals not only accept grafts but may also amplify microorganisms of human origin such as human immunodeficiency virus (HIV).[14] Human cell lines that are intended for use in animals should be screened for both rodent and human pathogens.

Opportunistic and emerging agents

Various microorganisms that do not usually cause clinical signs in immunocompetent animals may cause disease in immunodeficient animals or in animals whose resistance is lowered, for example, by other diseases, experimental procedures or drugs. Genetically-modified rodents may have unanticipated phenotypes, including overt or subtle immunomodulation, which result in disease induced by organisms thought to be commensals or previously unknown in that species. It may therefore be necessary to monitor such animals for opportunistic agents or commensals.[2,15] As almost any organism can be an opportunist,[16] provided it finds a suitable host or favourable circumstances, it is impossible to define a complete list of opportunistic agents for which animals should be monitored. Pathogenicity may be due to a variety of factors, including host, microbial, environmental, or combinations thereof.[17]

Emerging agents that affect animal health and research may be discovered at any time. Once

Table 3. Recommended infectious agents to monitor and frequencies of monitoring for laboratory mice (*Mus musculus*).

	Every 3 months	Annually
Viruses		
Mouse hepatitis virus	x	
Mouse rotavirus	x	
Murine norovirus	x	
Parvoviruses:		
Minute virus of mice	x	
Mouse parvovirus	x	
Theiler's murine encephalomyelitis virus	x	
Lymphocytic choriomeningitis virus		x
Mouse adenovirus type 1 (FL)		x
Mouse adenovirus type 2 (K87)		x
Mousepox (ectromelia) virus		x
Pneumonia virus of mice		x
Reovirus type 3		x
Sendai virus		x
Bacteria		
Helicobacter spp.	x	
If positive, speciation for *H. hepaticus, H. bilis* and *H. typhlonius* is recommended		
Pasteurella pneumotropica	x	
Streptococci β-haemolytic (not group D)	x	
Streptococcus pneumoniae	x	
Citrobacter rodentium		x
Clostridium piliforme		x
Corynebacterium kutscheri		x
Mycoplasma pulmonis		x
Salmonella spp.		x
Streptobacillus moniliformis		x
Parasites		
Endo- and ectoparasites (reported to the genus level)	x	
Additional agents*		
Viruses:		
Hantaviruses		
Herpesviruses (mouse cytomegalovirus, mouse thymic virus)		
Lactate-dehydrogenase elevating virus		
Polyomaviruses (mouse polyomavirus, K virus)		
Bacteria and fungi:		
Cilia-associated respiratory bacillus		
Klebsiella oxytoca, Klebsiella pneumoniae		
Other *Pasteurellaceae*†		
Pneumocystis murina		
Pseudomonas aeruginosa		
Staphylococcus aureus		
Others as necessary		

All agents listed should be reported if found in diagnostic examinations irrespective of when they are found.
*Testing for these agents is optional and should be pursued if there is a specific need. Frequency of testing will depend on local circumstances.
†We acknowledge that the inclusion of the *Pasteurellaceae* family is controversial. Screening for the family can be conducted should the facility wish, and the difficulty of some commercial kits to correctly identify *Pasteurella pneumotropica*, as well as the fluidity of the correct phenotypic classification, should also be acknowledged.

Table 4. Recommended infectious agents to monitor and frequencies of monitoring for rats (*Rattus norvegicus*).

	Every 3 months	Annually
Viruses		
Parvoviruses:		
Kilham rat virus	x	
Rat minute virus	x	
Rat parvovirus	x	
Toolan's H-1 virus	x	
Pneumonia virus of mice	x	
Rat coronavirus/Sialodacryoadenitis virus	x	
Rat theilovirus	x	
Hantaviruses		x
Mouse adenovirus type 1 (FL)		x
Mouse adenovirus type 2 (K87)		x
Reovirus type 3		x
Sendai virus		x
Bacteria and fungi		
Clostridium piliforme	x	
Helicobacter spp.	x	
If positive, speciation for *H. bilis* is recommended		
Mycoplasma pulmonis	x	
Pasteurella pneumotropica	x	
Streptococci β-haemolytic (not group D)	x	
Streptococcus pneumoniae	x	
Cilia-associated respiratory bacillus		x
Pneumocystis spp.		x
Salmonella spp.		x
Streptobacillus moniliformis		x
Parasites		
Endo- and ectoparasites (reported to the genus level)	x	
Additional agents*		
Bacteria and fungi:		
Bordetella bronchiseptica		
Corynebacterium kutscheri		
Encephalitozoon cuniculi		
Klebsiella oxytoca, Klebsiella pneumoniae		
Other *Pasteurellaceae*†		
Pseudomonas aeruginosa		
Staphylococcus aureus		
Others as necessary		

All agents listed should be reported if found in diagnostic examinations irrespective of when they are found.

*Testing for these agents is optional and should be pursued if there is a specific need. Frequency of testing will depend on local circumstances.

†We acknowledge that the inclusion of the *Pasteurellaceae* family is controversial. Screening for the family can be conducted should the facility wish, and the difficulty of some commercial kits to correctly identify *Pasteurella pneumotropica*, as well as the fluidity of the correct phenotypic classification, should also be acknowledged.

Table 5. Recommended infectious agents to monitor and frequencies of monitoring for guinea pigs (*Cavia porcellus*).

	Every 3 months	Annually
Viruses		
Guinea pig adenovirus	x	
Guinea pig parainfluenza virus 3/Caviid parainfluenza virus 3	x	
Sendai virus	x	
Guinea pig cytomegalovirus		x
Bacteria and fungi		
Bordetella bronchiseptica	x	
Corynebacterium kutscheri	x	
Streptococci β-haemolytic (not group D)	x	
Streptococcus pneumoniae	x	
Clostridium piliforme		x
Encephalitozoon cuniculi		x
Salmonella spp.		x
Streptobacillus moniliformis		x
Parasites		
Endo- and ectoparasites (reported to the genus level)	x	
Additional agents*		
Bacteria and fungi:		
Chlamydophila caviae		
Cilia-associated respiratory bacillus		
Dermatophytes		
Pasteurellaceae		
Pseudomonas aeruginosa		
Staphylococcus aureus		
Yersinia pseudotuberculosis		
Others as necessary		

All agents listed should be reported if found in diagnostic examinations irrespective of when they are found. *Testing for these agents is optional and should be pursued if there is a specific need. Frequency of testing will depend on local circumstances.

discovered, such agents present challenges to HM programmes because it is necessary to develop diagnostic assays and an understanding of the agent's epidemiology and transmission routes. In addition, time is needed to fully understand a newly discovered agent's effect on health and research. For these reasons, caution should be exercised before adding such organisms to a monitoring list.

Prevalence of infectious agents

Prevalent agents pose a higher risk of contamination than rare agents. Prevalence will vary depending on the animals' or biological materials' intrinsic characteristics, but also on the development and application of biocontainment methods, diagnostic tools and preventive or therapeutic measures. Prevalence data may be helpful in deciding which agents to monitor.[18–24] Local prevalence of an infectious agent may also depend on numerous other factors, such as the strain, immune status, age and sex of the animals, and the local conditions in each unit, such as open cages or microisolation cages, intensity of animal movement within and between facilities, and working routines.

Biological materials

Biological materials can potentially contain the same organisms, notably intracellular microorganisms, present in live animals.[25] For example, it has been shown that embryonic stem cells are susceptible to persistent infection with mouse hepatitis virus and may produce viruses.[26,27] Microorganisms can also be transmitted by materials such as monoclonal antibodies[28] and viral stocks.[29] In addition, murine germplasm should be considered as a potential source of infection.[30,31] More

Table 6. Recommended infectious agents to monitor and frequencies of monitoring for hamsters (*Mesocricetus auratus*).

	Every 3 months	Annually
Viruses		
Lymphocytic choriomeningitis virus	x	
Sendai virus	x	
Bacteria		
Pasteurella pneumotropica	x	
Clostridium piliforme		x
Corynebacterium kutscheri		x
Helicobacter spp.		x
Salmonella spp.		x
Parasites		
Endo- and ectoparasites (reported to the genus level)	x	
Additional agents*		
Viruses:		
Hamster polyomavirus		
Pneumonia virus of mice		
Bacteria and fungi:		
Encephalitozoon cuniculi		
Lawsonia intracellularis		
Other *Pasteurellaceae*†		
Others as necessary		

All agents listed should be reported if found in diagnostic examinations irrespective of when they are found.
*Testing for these agents is optional and should be pursued if there is a specific need. Frequency of testing will depend on local circumstances.
†We acknowledge that the inclusion of the *Pasteurellaceae* family is controversial. Screening for the family can be conducted should the facility wish, and the difficulty of some commercial kits to correctly identify *Pasteurella pneumotropica*, as well as the fluidity of the correct phenotypic classification, should also be acknowledged.

recent reports[25,32] suggest that the incidence of infectious agents in biological materials has markedly decreased over the past decades, but the risk still exists especially for those biologicals that have been stored for a long time and the source of which is ill-documented. For example, outbreaks of ectromelia in the USA caused by contaminated serum[33,34] underline the risk of agent transmission by biological materials.

Animals for testing and sampling

The choice of animals and samples to test is important for accurate HM programme results. Animals resident within a unit give the most reliable data on the microbiological status of a particular unit and should be used for HM wherever possible. In microbiological units consisting of two or more rooms, the sample should comprise animals from as many rooms as possible. It is important to note that each IVC can represent a microbiological subunit of the rack where they are placed and therefore as many cages as possible should be sampled.

In addition to those scheduled for routine monitoring, sick and dead animals or samples from these animals should be submitted for examination. This may apply to animals showing unexpected phenotypes in breeding facilities, as well as to experimental animals. A necropsy can allow the investigator to distinguish between effects caused by the experimental protocol and those caused by infection. The outcome of the necropsy may prompt an increase in the sample size or frequency of monitoring, or give rise to additional agent screening.

Resident animals

In a breeding facility containing at least 100 animals of the same strain or stock, and kept in open cages under conventional handling procedures, the so-called 'ILAR formula'[35,36] can be used to estimate the sample size in

Table 7. Recommended infectious agents to monitor and frequencies of monitoring for rabbits (*Oryctolagus cuniculus*).

	Every 3 months	Annually
Viruses		
Rabbit haemorrhagic disease virus (RHDV)*	x	
Rabbit rotavirus	x	
Bacteria and fungi		
Bordetella bronchiseptica	x	
Clostridium piliforme	x	
Encephalitozoon cuniculi	x	
Pasteurella multocida	x	
Cilia-associated respiratory bacillus		x
Salmonella spp.		x
Parasites		
Endo- and ectoparasites (reported to the genus level)	x	
Additional agents†		
Viruses:		
Adenovirus		
Coronavirus		
Myxomatosis virus		
Bacteria and fungi:		
Clostridium spp.		
Dermatophytes		
Escherichia coli (enteropathogenic strains)		
Other *Pasteurellaceae*		
Pneumocystis oryctolagi		
Staphylococcus aureus		
Treponema paraluiscuniculi		
Others as necessary		

All agents listed should be reported if found in diagnostic examinations irrespective of when they are found.
*In countries free from RHDV, antigen may not be allowed to enter the country. Sera may need to be shipped to remote laboratories for testing.
†Testing for these agents is optional and should be pursued if there is a specific need. Frequency of testing will depend on local circumstances.

order to assess its microbiological status. Animals of all ages and both sexes should be sampled, due to their differing susceptibility to agents. The animals should be taken from different locations and cages within the microbiological unit.

The 'ILAR formula'[35,36] is applicable only if certain circumstances are met. See http://lan.sagepub.com/suppl/DC1 for Appendix 2, which outlines the conditions under which the ILAR formula may be applied. These include a population of at least 100 animals where infections can spread and be distributed freely. The ILAR formula is not appropriate to define the size of the samples for monitoring small animal colonies kept in isolators, IVCs or other cage-level containment.

Sentinel animals

In some experimental and breeding units a number of factors, such as housing conditions, immunodeficiency of resident animals, or insufficiency of animals may not allow for the direct sampling of resident animals. HM may then be carried out on sentinels. Sentinels are exposed to animals of the same (or another) species to evaluate their microbiological status and should be submitted for testing after a sufficient exposure period. They are often introduced from external sources, but it is also acceptable to use the term for animals that are taken from the resident population and then widely exposed to other resident animals. If sentinels are not bred within the unit that is being monitored, they must be obtained from a

population free of the agents and antibodies to be monitored.

Sentinels may be either indirect (animals that are exposed to materials soiled by resident animals, such as bedding, water, or feed) or direct (animals that are placed in the same cage as the resident animals). Sentinels should be housed in the same unit as resident animals for at least six weeks before testing, using the same husbandry conditions. Longer exposure periods (10–12 weeks) are better since more time may be necessary for infection and/or seroconversion to certain agents such as *Mycoplasma pulmonis* and *Pasteurella pneumotropica*. Retention of sentinels may also allow for a low prevalence infection in cage-level containment housing to reach a prevalence where a sentinel might detect it.

Generally, sentinel animals should be of the same animal species as the population to be examined. Occasionally, exotic species of rodents are housed in laboratories. In this case, sentinels from a common rodent species are used when the concern is what the exotic animals might transmit to common laboratory rodents. For example, laboratory mice or rats might be used as sentinels for naked mole rats. A variety of stocks and strains of animals can be effectively used as sentinels. Immunocompetent outbred animals are frequently chosen since they are robust and susceptible to a wide range of agents. Inbred or mutant strains vary in their susceptibility to specific infectious agents,[37,38] but could be used as long as this varying susceptibility is taken into consideration, where known. Similarly, the animals' age and sex may influence susceptibility to infection with certain agents.[37,39] If serological methods are to be used, the sentinel animals should be immunocompetent young animals, which usually mount a good immune response.

Immunodeficient animals are generally more susceptible to infectious agents than immunocompetent animals but may not seroconvert effectively, or at all. They may sustain persistent infections and thus may allow the detection of agents that are usually eliminated by immunocompetent sentinels and detected by direct methods, such as *Pneumocystis murina* or *Corynebacterium bovis*. A disadvantage of immunodeficient animals is that they may serve as a source of persistent infection for the other resident animals.

Sentinel animals may acquire infectious agents present in a microbiological unit by indirect or direct contact with colony animals. The most common method of indirect exposure is via dirty bedding. This entails keeping sentinels on soiled bedding taken from an adequate number of cages from the microbiological unit under examination. Dirty bedding sentinels should be housed on at least 50% dirty bedding and the bedding should be changed at least weekly. The number of cages supplying each sentinel cage should be determined by the person overseeing the HM programme. Typically, one sentinel cage per 50–80 IVCs is used. Regular changes of donor cages may then give insight into the microbiological status of the unit. The reliability of this method is dependent on the choice of sentinel, the route(s) by which the infectious agent is shed, the duration of shedding, the concentration of the excreted agent, the stability of the agent after it is shed, the volume of soiled bedding transferred, and the frequency of the bedding transfer.[40–42] Sentinel animals may also be fed from used feeding devices and drinking bottles or even housed in cages previously occupied by resident animals. The testing of exhaust filters by polymerase chain reaction (PCR)-based methods may also be considered for monitoring exhaust air from individual cages or an entire IVC rack.[40,41] In any case, sentinel animals should be handled last during routine husbandry procedures.

Not all agents can be easily transferred via soiled bedding (e.g. LCMV, Sendai virus, *Pasteurella pneumotropica*)[13,41,43] or exhaust air (e.g. *Helicobacter* spp., mouse rotavirus, mouse parvovirus)[41] and therefore in some circumstances sentinels may be kept in direct contact with the animals to be monitored by placing them in the same cage. The use of direct contact sentinels may allow or at least increase the chance of finding certain agents. Contact sentinels should be compatible with the animals to be monitored. The movement of contact sentinels among cages may spread an agent to previously uninfected cages and should be avoided.

If suggested FELASA testing frequencies are followed, new sentinels will be placed at least quarterly. A sufficient number of exposed sentinels to allow for confirmatory testing should always be present in the microbiological unit during a monitoring period; sentinel cages often contain 2–5 animals. The number of sentinels per unit depends on many factors including type of housing, risk of acquiring infections or detection methods, and should be determined by the person responsible for the institution's HM programme.

In summary, indirect sentinel methods alone cannot reliably detect all infectious agents, but direct sentinel use or resident animal sampling may not always be possible. When cage-level containment housing (e.g. IVCs) is used, it is difficult to gain a complete overview of the unit's infectious agent status. Therefore, a complex course of action is necessary in which the optimal HM programme should be determined on an individual basis.

Assays and interpretation

Testing should be performed under supervision of staff with an academic degree in veterinary medicine,

medicine or microbiology, who also have experience in laboratory animal diagnostics and laboratory animal science at the level of FELASA Category D (or equivalent).[44] FELASA advocates accreditation of diagnostic laboratories and HM schemes according to FELASA guidelines[8] although neither is required. Each animal facility should also identify a person with sufficient understanding of the principles of HM as the individual responsible for interpreting the results of laboratory tests. Laboratory reporting is not always sufficient and additional information may thus be required in order to interpret positive as well as negative results.

The presence of an infectious agent in a population can be detected by a variety of direct or indirect methods. A full necropsy of euthanized animals allows for the systematic examination of the carcass for abnormalities and the inspection of organs for the presence of gross abnormalities. Routine histopathology on grossly normal organs is not generally necessary. The aetiology of gross changes should be further investigated by additional methods, as appropriate. Histopathology may also be used to detect or confirm infections by uncultivable bacteria, such as *Clostridium piliforme*, or extraintestinal parasites such as *Klossiella* spp. Lesions may support positive serology results, or may reveal organisms not included in routine screening programmes. This may be particularly important in immunodeficient animals, where a variety of organisms can cause opportunistic infections. General guidelines for necropsy and sampling for histopathology and microbiology in rodents and rabbits have been published.[45]

The skin and fur of animals should be examined for evidence of ectoparasites. Endoparasites can be diagnosed by PCR, direct visual examination, or smears of intestinal contents, after flotation and microscopy of faeces, and on adhesive tapes used for sampling around the anus. Identification of parasites should proceed as far as possible to the species name.

Serological methods are widely used for screening for viruses, certain bacteria (e.g. *Clostridium piliforme*, *Mycoplasma pulmonis*) and a limited number of other organisms, such as *Encephalitozoon cuniculi*. Suitable serological methods include bead-based fluorescent multiplexed immunoassays (MFI, or MFIA®), the enzyme-linked immunosorbent assay (ELISA), the indirect immunofluorescence assay (IFA), and the haemagglutination inhibition (HAI) test. Western blots are not suitable for routine screening, but are highly specific and sensitive, so are occasionally used for confirmation.

Direct detection of agents by PCR is useful for confirmation of positive or equivocal serological results, for the early detection of agents before seroconversion occurs, or for the screening of immunodeficient animals. It requires careful selection of animals and tissues for evaluation since target organisms must be present at the time of testing in the specimen evaluated. PCR can also be used to evaluate the risk of agent transmission from animals, for example by testing excretions for shedding of organisms. Furthermore, PCR assumes a more prominent role in the screening of biological materials where it replaces conventional antibody production tests.[46]

Culture techniques are usually employed for the detection of most bacterial and fungal agents. Samples are commonly taken from the genital mucosa, the large intestines, nasopharynx, and trachea; and other sites may be sampled as necessary. Lesions suspected to be of bacterial origin should be cultured. The skin of rabbits and guinea pigs may be examined for dermatophytes. Identification of relevant bacteria should proceed to the species level where necessary. Commonly used kits for the identification of human and veterinary pathogenic bacteria may fail to correctly identify bacterial strains from laboratory animals (e.g. *Pasteurella pneumotropica* and *Citrobacter rodentium*). PCR is now routinely used for the detection and identification of some bacteria, most notably *Helicobacter* spp., which are otherwise difficult to cultivate or identify to a species level with classical culture techniques. Serological methods exist for the detection of various bacterial pathogens[47] but there is a higher risk of false-positive reactions when compared with viral serology, due to the more complex antigenic structure of bacteria.

The use of a suitable test method does not necessarily imply a reliable test outcome. At a minimum, reliability depends on the sensitivity and specificity of the test, as well as the sample's true representation of the microbiological unit. Since positive results may prompt drastic measures in a facility, including culling of animals, facility disinfection and interruption of experiments, it is important to confirm any positive results by using other methods at least as specific as the first one. The results should be confirmed by repeated sampling and testing of resident animals or sentinels. If possible, positive results should also be confirmed by another laboratory. Experience shows that results obtained from different diagnostic laboratories may vary. Conflicting or borderline results should be investigated further until a conclusion on agent status can be reached. A health management action plan should be put in place while waiting for confirmatory results in order to avoid the potential spread of contaminants. Confirmation processes in progress should be mentioned as additional information in the HM report.

Every assay can produce false-positive and false-negative results. Prevalence data may help in the estimation of the predictive value of test results, i.e. they are helpful in knowing how much weight to accord a positive test result. Rare agents are less likely to be

found in a population, and therefore less likely to produce true positives. When a number of sera are subjected to a battery of serological tests, some false-positive test results must be expected, even when tests are highly specific, e.g. 95%.[48,49] The presence of antibodies in animal serum generally indicates a current or previous infection, but may also be due to maternal antibodies, vaccination or a cross-reaction. PCR can also give false-positive results, for example due to sample contamination or non-specific amplification of DNA.

If serological tests are used, negative results mean only that antibody activity to the microorganisms monitored has not been demonstrated in the animals screened by the test(s) used. The results are not necessarily a reflection of the status of all the animals in the unit. It takes some days or weeks for animals to produce an antibody response detectable with routine serological tests, therefore serological test results will be negative during the early stages of infection. Studies on rodents infected with some prevalent agents, such as parvoviruses, have shown that some infected animals are poor responders and may seroconvert slowly or not at all.[37,38] Seroconversion also depends on the dose, biological attributes of the agent and the genetic composition, age and immune status of the infected animal. Equivocal results should be evaluated carefully in light of the above.[38,50] PCR can also give false-negative results (e.g. due to the presence of polymerase inhibitors) as can bacterial cultures. Bacteria responsible for subclinical infections may be present only in low numbers and may not be detected, either due to overgrowth of other bacteria on conventional culture media, or because they perish in transit to the testing laboratory. Sampling from recently killed animals and the use of selective and transport media respectively may help in overcoming these potential problems.

Health monitoring report

It is important to note that an HM report is not a laboratory report. The laboratory report consists simply of results provided by the testing laboratory on samples from tested animals. This means that it does not allow for conclusions about the microbiological status of the complete unit because it lacks information provided in the full HM report.

HM reports should be produced by the person in charge of the HM programme. They should be made available to interested parties within an institution and when animals are shared between institutions. Data reflecting the health status of animals used in an experiment are part of the experimental work and should therefore be evaluated for their influence on the results of experiments and included in scientific reports and publications as part of the animal specification.

HM reports should, as far as possible, be presented in a format standardized in layout and content. A joint working group comprised of members of FELASA and AALAS is currently (2013) evaluating the potential for a common health report to be used for international transfer. Table 8 contains suggested information to be presented in a health report. A sample HM report is shown as Figure 1.

An agent must be declared to be present on the health report if it is identified and confirmed in one or more of the animals screened. Agents known to be present need not be monitored at subsequent screens

Table 8. Recommended information for a health monitoring (HM) report.

- Unit name and housing condition (non-barrier, barrier, IVC, isolator).
- Identification of all species and strains/stocks present within the unit. Where multiple species are reared in the same barrier, one HM report should be available per species.
- Date of the latest investigation and date of issue of the report.
- Test frequency for each agent.
- Names of agents for which monitoring is undertaken, listed alphabetically within their microbial category and identified to species level where necessary.
- Test method used for each agent and name of testing laboratory.
- Results of the latest investigation and all investigations as far back as practically possible (ideally since unit inception), but not less than 18 months (expressed as number of positive animals/number of animals examined). Results of testing not included in the standard HM programme should be added as supplementary information (e.g. disease diagnoses).
- Results of pathological examinations should be recorded as: lesions were/were not observed in the animals examined. Pathological changes should be listed separately for each species and strain/stock.
- A space for comments. If colonies have been treated for an agent, it should be noted here. Date of first and latest findings of an agent could also be included here.
- Name and contact details of the person responsible for devising the HM programme.
- Description of the overall HM programme (e.g. through a link to permanent location or a cover letter).

HEALTH MONITORING REPORT

Unit number/name: Date of report issue:
Species: Housed strains/stocks:
Housing type:

Health monitoring is conducted in accordance with FELASA recommendations. Further information about the overall health monitoring programme is available on request or at the following website: [place URL here]

	Test frequency	Date of last results	Last results	Testing laboratory	Test method	Historical results (ideally from inception, at least ≤ 18 months)
Viruses						
[Agents listed in alphabetical order]			[Number of positive animals/ number examined]			
Bacteria and fungi						
[Agents listed in alphabetical order]						
Parasites						
[Agents listed in alphabetical order]						
Anatomopathology						
Gross examination(s)			[Lesions were/ were not observed in the animals examined]			
Histopathology of significant gross lesions						

Comments: [e.g. notations about treatment or other significant information]

This document (electronically) signed by laboratory personnel.

Name & contact details of the person responsible for the health monitoring programme design.

Figure 1. A sample health monitoring report. Other formats are acceptable if the information is presented clearly and simply.

provided that they are declared in the health report. The unit must continue to be reported as positive at subsequent screens until the organism has been eradicated, for example by means of hysterectomy or embryo transfer or restocking with animals from another source. Eradication of the infection(s) will be confirmed by subsequent testing.

Given the statistical limitations of the results, the HM report should not be the sole basis of the decision to allow the entry of imported animals to a facility. The health history of the facility of origin and its HM programme, as well as the risks of possible contamination, should also be taken into account. For an example of an HM programme description, please see Appendix 3 (http://lan.sagepub.com/suppl/DC1). In addition, the health status of animals may change during transport. Facilities should evaluate the risks inherent in the introduction of animals and develop an appropriate plan (e.g. quarantine and testing process).

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Appendix 1: Comments on agents

These comments have been added because:

- some agents, for which monitoring was recommended earlier, were removed from the list or the frequency of monitoring was changed;
- some new agents have been added.

The information given here should help readers of the recommendations to better understand why monitoring for specific agents is recommended or why changes were made (compared with previous recommendations). Therefore, very basic information is given on most agents. For details, the reader is advised to consult specialists in the field and the scientific literature. A selected bibliography is provided at the end of Appendix 1.

Bacteria, fungi

Bordetella bronchiseptica: Gram-negative bacterium associated with lesions in the airways of guinea pigs and other species, like pigs, dogs and cats. In rabbits, subclinical disease is common. It has low significance in mice and rats.

Cilia-associated respiratory (CAR-) bacillus: Gram-negative filamentous bacterium associated with chronic respiratory disease in mice, rats, rabbits and other species. *CAR-bacillus* does not grow on bacterial culture media. It is often a co-pathogen in multifactorial infections together with *Mycoplasma*, other bacteria and viruses. Cage to cage transmission of the infection is slow and transmission to sentinels by dirty bedding is unreliable.

Chlamydia spp.: Obligate intracellular bacteria causing persistent, usually subclinical infections. Their significance is uncertain but seems to be low. *Chlamydophila caviae* causes conjunctivitis and pneumonia in guinea pigs, and may have zoonotic potential Accurate serological tests for screening are available only at a few laboratories.

Citrobacter rodentium: Gram-negative bacterium that has been reported to lead to transmissible colonic hyperplasia in mice.

Clostridium piliforme: Gram-negative, obligate intracellular rod, causative agent of Tyzzer's disease in several animal species. Gerbils are highly susceptible. *C. piliforme* does not grow on bacterial culture media. Stress may activate latent disease and immunosuppression has been used to demonstrate the presence of this agent in animals. The results of serological testing should be confirmed by another test method such as polymerase chain reaction (PCR). Histopathology is appropriate for diagnosing Tyzzer's disease but is insensitive for screening laboratory animal colonies for subclinical infections of *C. piliforme*.

Corynebacterium bovis: Gram-positive bacterium, aetiological agent of 'scaly skin disease' or 'corynebacterial hyperkeratosis' of *Foxn1*^{nu} mice. *C. bovis* may also cause lesions in mice with fur, e.g. *Prkdc*^{scid} mice,

and may be carried asymptomatically by immunocompetent mice.

Corynebacterium kutscheri: Gram-positive bacterium, aetiological agent of 'pseudotuberculosis'. Subclinical and symptomatic infection (pneumonia) has mainly been detected in mice, rats and guinea pigs.

Dermatophytes: Dermatomycoses have zoonotic potential. Infections with *Microsporum* spp. and *Trichophyton* spp. occasionally occur in guinea pigs and rabbits. Subclinical disease is common and metabolic stress or adverse ambient factors (e.g. pregnancy, overcrowded animal room, high relative humidity) may predispose for disease outbreaks.

Encephalitozoon cuniculi: Gram-positive organism with zoonotic potential. It is classified as a microsporidian (fungus), but in the past it has been considered as a protozoan. *E. cuniculi* is most common in rabbits. It causes multifocal nephritis and encephalitis (mostly subclinical). Lesions in guinea pigs and rodents are uncommon. Infectious spores are excreted in urine.

Escherichia coli: Ubiquitous Gram-negative bacterium found in the intestines of healthy animals and humans. Colibacillosis in animals is associated with diarrhoea, dehydration and mortality, predominantly in young animals. In rabbits, *E. coli* infection can cause outbreaks of diarrhoea with high mortality and aggravate other enteric diseases, e.g. coccidiosis.

Francisella tularensis: Gram-negative coccobacillus causing natural infections in wild lagomorphs and rodents. Other species and humans may also be infected. Transmission occurs by direct contact and indirectly (e.g. by ticks or contaminated water). *Francisella* may survive in carcasses for prolonged periods. Accidental transmission under laboratory work has been repeatedly reported (e.g. by inhalation and splashes to the conjunctiva).

Helicobacter spp.: This genus includes numerous species, some of which have the potential to induce clinical disease in laboratory animals or may have impact on animal experiments (e.g. *H. hepaticus*, *H. bilis* and *H. typhlonius*). The main habitat of *Helicobacter* in rodents is the large intestine, but their effects in research are widespread and not restricted to the gastrointestinal tract (e.g. influence on mammary tumour development).

Klebsiella spp.: Gram-negative rods, occasionally associated with generalized infections, genital lesions, pneumonia and suppurative processes in rodent and rabbits, both in primary and opportunistic infections.

Lawsonia intracellularis: Intracellular, argyrophilic *Campylobacter*-like organism that does not grow on bacterial culture media and causes proliferative enteritis (wet tail) in hamsters. Screening is not recommended as infection is supposed to lead invariably to clinical disease with characteristic lesions in the intestine.

Leptospira spp.: Monitoring for these zoonotic bacteria may be considered if laboratory animals are at increased risk of infection, for instance when using wild rodents or when contact with wild rodents is suspected. Seromonitoring is done by specialized laboratories as monitoring for several serotypes is necessary. Occurrence of *Leptospira* spp. in contemporary colonies is uncommon.

Mycoplasma spp.: *M. pulmonis* is the most relevant species in mice and rats. Screening is usually done by serology, but antibody response varies greatly between mouse and rat strains. Culture is difficult but may additionally detect various other *Mycoplasma* species.

Pasteurellaceae: Monitoring for all *Pasteurellaceae* may be performed. These bacteria stain Gram-negative. *Pasteurella pneumotropica* describes a genetically diverse group of organisms and commercial identification kits do not identify them properly. *P. pneumotropica* infections are commonly subclinical, but respiratory, ocular and genital lesions and mortality have been described in immunocompetent and immunodeficient animals, including mutants. *P. multocida*, the aetiological agent of pasteurellosis in rabbits and many other species of domestic animals, can cause enteritis, respiratory infection, septicaemia, etc. Pasteurellosis has become uncommon in modern laboratory rabbitries.

Pneumocystis spp.: Important fungal pathogens that may lead to clinical respiratory disease, emaciation and death in immunodeficient animals. Lesions in immunocompetent animals are transient. Histopathology may demonstrate organisms in clinical pneumocystosis and PCR may be used for detection of organisms in low-grade infections (e.g. in immunocompetent animals). Presently, one *Pneumocystis* species is recognized in laboratory mice (*P. murina*) and two species are recognized in laboratory rats (*P. carinii* and *P. wakefieldi*). *P. carinii* is the major species in rats and likely an aetiological agent of idiopathic lung lesions consistent with RRV (see 'Rat respiratory virus').

Proteus spp.: Gram-negative, pleomorphic, often rod-shaped bacteria commonly present in the intestines of healthy animals. Opportunistic infections have been described in mice.

Pseudomonas aeruginosa: Gram-negative, short rod that may cause clinical disease in immunocompromised hosts but has low significance in immunocompetent animals.

Salmonella spp.: Gram-negative, short rods infrequently found in laboratory animals. *Salmonella* has zoonotic potential and infected rodents and other hosts, including personnel, may be sources of infection.

Staphylococcus aureus: Gram-positive bacterium ubiquitous in rodent populations where there is direct contact between humans and animals. *S. aureus* has

zoonotic potential. *S. aureus* can be the causative agent of dermatitis, abscesses and other lesions, but it is also a secondary invader (e.g. wound infections). Lesions may attain a high prevalence in rodent and rabbit colonies.

Streptobacillus moniliformis: This Gram-negative, zoonotic agent can cause rat bite fever or Haverhill fever. Culture of the bacterium from asymptomatic animals is notoriously difficult. Rats are the natural host.

Streptococcus spp.: Gram-positive cocci (α-haemolytic *S. pneumoniae* and β-haemolytic other species) rarely induce clinical disease in immunocompetent individuals but are important primarily in immunodeficient animals. Lesions (e.g. pneumonia, lymphadenitis, serositis) occur most frequently in guinea pigs.

Treponema paraluiscuniculi: Gram-negative, spiral-shaped bacterium which does not grow on bacterial culture media. *T. paraluiscuniculi* causes rabbit syphilis or treponematosis, but the disease is subclinical in many rabbits. Rabbit syphilis has low significance in laboratory rabbits but is still prevalent in pet and wild lagomorphs.

Yersinia pseudotuberculosis: Guinea pigs are preferentially affected by this Gram-negative rod, but rats, rabbits and other species including humans are also susceptible. Subclinical disease is common. Animals with acute disease suffer from enteritis, whereas the chronic course is characterized by caseous necrotic lesions in lymph nodes and abdominal organs (pseudotuberculosis).

Parasites

Ectoparasites

Colonies of laboratory animals may severely suffer from ectoparasites (mites, lice and fleas). Clinical signs may range from none or mild alopecia and reddening of the skin to extreme pruritus with self-excoriation and deep ulceration of the skin. Ulcerations may then be complicated by secondary infections. Some ectoparasites induce allergic reactions or hyperplastic skin lesions (e.g. ear mange). Ectoparasites also produce numerous systemic adverse effects.

Mites: These are the most common ectoparasites in laboratory animals and may be grouped according to their living habits in (A) fur-dwelling mites, (B) surface-dwelling and burrowing mites, and (C) follicle-dwelling mites.

A. Fur-dwelling mites: *Myobia musculi* (mice, rarely rats) and *Myocoptes musculinus* (mainly mice) are the most prevalent mites in mice and rats. *Radfordia affinis* seems to infest only mice and *R. ensifera* seems to infest only rats. *Radfordia* spp. are morphologically similar to *M. musculi* and mice may be infested with both mite species. Mice are the only host for *Trichoecius rombousti* and clinical signs may be similar to those of other mites. Its occurrence in laboratory animals is uncommon. *Cheyletiella parasitivorax and Leporacarus gibbus* are becoming rare in laboratory rabbits, but infestations are common in domestic rabbits. *Cheyletiella* is zoonotic. In rare cases partial alopecia and fine gray–white scale on the skin surface can be observed, but the skin is not severely inflamed or pruritic.
B. Surface-dwelling and burrowing mites include *Notoedres musculi* in mice and *N. muris* in rats and other rodents. *N. muris* (rats) and *Psoroptes cuniculi* (rabbits) can cause hyperplastic ear mange lesions that are quite stressful for the animals. Guinea pigs are the host of *Trixacarus caviae*. Finally, although rare in laboratory animals, *Sarcoptes scabiei* infests numerous animal species, including rodents, and is a well-recognized zoonosis.
C. Follicle-dwelling mites include *Psorergates* and *Demodex*. *Psorergates simplex* causes small cystic lesions in the skin of mice, but it is rare today. *Demodex musculi* lives in the hair follicles of mice. Little is known about the life cycle of these mites. It is assumed to be similar to that of other mites. *D. musculi* is likely transmitted from the mother to pups during nursing, similar to *D. canis*. Demodicosis, *D. aurati* and *D. criceti* in hamsters, and *D. cuniculi* in rabbits are uncommon in modern laboratory animal colonies.

Lice: These occur in wild and pet rodents but have been eradicated from laboratory colonies. Sucking lice (suborder Anopleura) include *Polyplax serrata* (mice) and *P. spinulosa* (rats). Chewing lice (suborder Amblycera) are represented by *Gliricola porcelli, Gyropus ovalis* and *Trimenopon jenningsi* in guinea pigs.

Fleas: These are no longer found in well-managed animal facilities.

Endoparasites

Protozoa

Amoebae (*Entamoeba* sp.): *Entamoeba muris* is the only amoeba identified in laboratory mice and is considered as a commensal inhabitant found in the large intestine. Surveys of wild and laboratory mouse populations demonstrate a prevalence of between 5 and 55%. Organisms morphologically identical to *E. muris* are also identified in laboratory and wild rats and hamsters. Infections are subclinical and no examples of interference with research have been reported.

They might, however, be an indicator of hygiene failures or contact with wild or infected animals.

Flagellates

Chilomastix sp.: Infection with *Chilomastix mesnili* may cause severe symptoms in humans, but no reports exist about symptoms, disease or possible impact on research in rodents (*C. bettencourti*).

Giardia muris: This is the only flagellate in mice considered to be pathogenic. It is also common in other rodents (rats) and causes subclinical infection in immunocompetent animals. Immunocompromised mice lose body weight and fail to thrive. These clinical signs can also be observed in mice infected as weanlings, presumably due to a less mature immune system. *Giardia muris* in hamsters is morphologically indistinguishable from that in mice. *G. duodenalis* (pet and farm rabbits) has zoonotic potential.

Enteromonas caviae and *Monocercomonas caviae*: These are apathogenic and can be found in the faeces of guinea pigs. These flagellates are not transmittable to rats.

Spironucleus sp.: Recent surveys of laboratory and wild mice suggest that the prevalence ranges from 4.1 to 38.6%. No information is available on the prevalence in other rodent species. *Spironucleus* is often associated with other infective agents (e.g. MHV) and may then induce clinical signs and have impact on various types of experiments. It causes enteritis in immunodeficient animals. *Spironucleus* has a simple and direct life cycle, the minimal infective dose is one cyst. Insufficient information is available on the transmission of these flagellates between different rodent species (mouse, rat, hamster).

Trichomonads (*Tritrichomonas muris*): Only a few publications show that these flagellates have impact on physiological parameters of their host. They are, however, likely to be species-specific and thus might be an indicator of a leak in the barrier system or the existence of direct or indirect contact with wild rodents.

Coccidia

Cryptosporidium spp.: These are gastrointestinal parasites found in rodents, rabbits and numerous other species, including humans. *C. parvum* is zoonotic and the less prevalent *C. cuniculus* has zoonotic potential. Outbreaks in humans and farm animals are frequently caused by ingestion of contaminated water or food.

Eimeria spp.: These host-specific protozoans are common pathogens in rabbits and guinea pigs and may cause enteritis, cholangiohepatitis and death, primarily in young animals. Infections with *Eimeria* spp. may also occur in mice and rats but are uncommon.

Klossiella spp.: These are found in kidney tubules or endothelial cells of blood vessels in mice (*Klossiella muris*) and guinea pigs (*K. cobayae*). The infection is clinically occult but lesions in the kidneys are usually visible macroscopically. Diagnosis is made histologically by finding replicating forms within the glomeruli or renal tubules epithelium.

Toxoplasma gondii: Monitoring is not recommended because infectious forms are only excreted by Felidae; spread of the infection within rodent and rabbit colonies does not occur. Interference with research due to endemic toxoplasmosis has not been reported for mice.

Helminths

Cestodes: Most species require an intermediate host and are therefore unlikely to be found in well-managed animal facilities. Some species, however, may have a direct life cycle by ingestion of eggs and have been detected in rodent colonies (e.g. *Rodentolepis nana*, formerly *Hymenolepis nana*). Although *R. nana* is considered to be a zoonotic parasite, the human and rodent strains may be different and not cross-infective.

Rodentolepis microstoma: This resides in bile ducts and normally requires an intermediate host. A direct life cycle is possible in immunocompromised animals.

Taenia taeniaeformis: This is the feline tapeworm, and the mouse is an intermediate host. It is not expected to be found in laboratory animals.

Nematodes: Several species have been reported in laboratory animals. They may colonize different parts of the intestinal tract (e.g. stomach, liver, caecum, colon) and even the urinary bladder. Due to differences in their life cycles and different predilection sites in their hosts, several detection techniques (e.g. examination of the entire gastrointestinal tract, perianal examination with cellophane tape, flotation, wet mount of caecum contents) may be necessary to detect or exclude adult worms and parasitic larval stages.

Oxyurids (pinworms): These have a direct life cycle and are prevalent in mice and rats (*Aspiculuris tetraptera*, *Syphacia muris*, *S. obvelata*). Infestations are considered to be clinically silent in immunocompetent animals. A variety of non-specific signs have been attributed to heavy infestation but association with other infectious agents in such cases could not be excluded. Infestation with pinworms may interfere with research; the most important effect is modulation of the immune system. Syrian hamsters have their own Oxyuridae (*S. criceti*, *S. mesocriceti*). *Passalurus ambiguus*, the common pinworm of rabbits, is rarely found in laboratory rabbits and seems to be non-pathogenic.

Trichosomoides crassicauda: This is known as the 'bladder threadworm'. It is embedded in the mucosa of the urinary bladder of rats and causes epithelial hyperplasia with a lack of inflammation. In rare cases, nephritis, eosinophilia and pulmonary granuloma formation can be observed. Natural infection is usually inapparent.

Trichostrongyloidea (*Graphidium strigosum, Obeliscoides cuniculi, Trichostrongylus* spp.): These are

common in wild rabbits and occasionally found in domestic rabbits but not in contemporary laboratory rabbits. Infestation is often subclinical; severe infestations can be associated with haemorrhagic or chronic gastritis, anaemia, weight loss, and possibly death.

Trichuris muris: This is rare in laboratory mice but common in wild mice. The infection is used as a model to study host–parasite interaction. Effects on research may include modulation of the immune system or in case of heavy infestation the mice may suffer from anaemia.

Viruses

Coronaviruses (MHV in mice, RCV/SDAV in rats): These occur frequently and are strongly immunomodulating. Multiple strains that differ in virulence and organotropism have been identified. Infections are usually self-limiting but may be persistent in immunodeficient animals.

Guinea pig adenovirus: This has been identified repeatedly as a causative agent of respiratory disease or death in guinea pigs. The virus cannot be propagated in cell culture, and antigen for serological tests is therefore difficult to obtain. Mouse adenovirus (K87 or FL) is commonly used as an antigen to test guinea pig colonies for antibodies to guinea pig adenovirus, but there is conflicting information on the degree of cross-reactivity between mouse and guinea pig adenoviruses and the validity of these tests.

Guinea pig cytomegalovirus (GpCMV): This species-specific virus rarely causes clinical signs in immunocompetent guinea pigs. Vertical transmission of the virus is considered common. Seromonitoring results can be confirmed by antigen detection in organs of animals under severe immunosuppression. There is no cross-reactivity with other herpesviruses.

Guinea pig parainfluenza virus 3/*Caviid parainfluenza virus 3*: These paramyxoviruses are closely related genetically and subclinically infect guinea pigs. Their impact on research is mainly through pulmonary lesions and respiratory hyperreactivity to smooth muscle contractile substances in clinically healthy guinea pigs. Serological cross-reactivity with other paramyxoviruses can occur.

Hamster polyomavirus: Lymphomas and skin tumours with hair follicle differentiation, predominantly in young hamsters, are characteristic lesions of this viral infection. It seems to be prevalent among pet hamsters in European countries.

Hamster parvovirus (HaPV): Adult hamsters develop clinically silent infections but infection of suckling and weanling Syrian hamsters may result in severe and often lethal diseases. HaPV shows genetic similarity to MPV-3, suggesting that a cross-species transmission occurred (where the mouse probably served as the natural host). Monitoring is recommended as soon as an antigen is available.

Hantaviruses: Wild rodents are natural reservoirs for this group of zoonotic viruses. Laboratory rats and rat material have repeatedly been the source of Seoul serotype Hantavirus infections in research personnel. None of the many other serotypes (e.g. Puumala) has so far been detected in laboratory animal colonies. Hantavirus infections in rats are inapparent.

K virus (mouse pneumonitis virus): This occurs rarely, if at all, in contemporary laboratory mouse colonies.

Kilham rat virus (KRV, RV): See Parvoviruses.

Lactate dehydrogenase elevating virus (LDV): This infects mice only and is transmitted within a population vertically or by direct contact (blood). The most important mode of transmission is by experimental procedures (injections, animal-to-animal passages of tumours, microorganisms, parasites, etc.). It is unlikely to be found in breeding units, but it is an important contaminant of biological materials after animal passages. It should be included in monitoring programmes for biological materials and mice if such materials are passaged in mice.

Lymphocytic choriomeningitis virus (LCMV): Only mice, hamsters and New World primates are known to transmit this zoonotic virus, but other species (e.g. rabbits, guinea pig, rats) also seem to be susceptible to experimental infection. Detection of enzootic infection in mice by serology may be difficult (depending on the mode of infection) due to immunotolerance.

Minute virus of mice (MVM): See Parvoviruses.

Mouse adenovirus: It was shown that both strains of mouse adenovirus do not always cross-react in serological tests. Therefore, both strains (FL, K87) should be used as antigens. Positive reactions have also been found in rats, and it is recommended that rats are also monitored.

Mouse cytomegalovirus (MCMV): The prevalence of this virus in contemporary laboratory mouse colonies is thought to be negligible except in instances in which colonies may have been contaminated by wild mice.

Mouse hepatitis virus (MHV): See Coronaviruses.

Mouse parvovirus (MPV): See Parvoviruses.

Mouse polyomavirus: This occurs rarely, if at all, in contemporary laboratory mouse colonies.

Mousepox (ectromelia) virus: Recent infections came mostly from contaminated biological materials (sera). Susceptibility and antibody response greatly differ among mouse strains.

Mouse rotavirus (EDIM): 'Epizootic diarrhoea of infant mice' describes the clinical syndrome associated with infection during the first two weeks of life. Infections are usually self-limiting in

immunocompetent animals. Mouse rotavirus has been found in many mouse colonies in recent years and does not infect other species.

Mouse thymic virus (MTV): This occurs rarely, if at all, in contemporary laboratory mouse colonies.

Murine norovirus (MNV): This has only recently been described and is currently the most commonly detected viral agent in laboratory mice. The infection tends to persist and does not induce clinical signs in immunocompetent and most immunodeficient mice. MNV has immunomodulatory properties. It is not known to cross species barriers.

Parvoviruses: These are among the most common viruses of laboratory rodents. In addition to well-known parvoviruses (MVM, KRV, H-1), additional species have been found during the last two decades (mouse parvovirus, MPV; rat parvovirus, RPV; rat minute virus, RMV). Different strains exist for these viruses, and propagation in cell culture is not easily possible. Therefore, antigens are difficult to obtain, and only a few laboratories are able to test for these agents by specific tests. Rodent parvoviruses possess immunomodulatory properties and might affect a variety of studies. They are relatively common contaminants of animal tissues and transplanted tumour cell lines.

Pneumonia virus of mice (PVM): This infects mice and rats. Its prevalence in contemporary laboratory animal colonies seems to be low.

Rabbit enteric coronavirus: Infections seem to occur frequently in rabbitries, but the virus has not been isolated (hence monitoring is only possible by electron microscopy).

Rabbit haemorrhagic disease virus (RHDV): This highly contagious calicivirus causes high mortality in rabbit populations. However, apathogenic caliciviruses exist which interfere with serological tests. Positive serological reactions for RHDV may therefore be caused by cross-reaction with such virus strains and should be interpreted with care.

Rabbit parvovirus: Infections seem to occur frequently in rabbitries. Monitoring is recommended as soon as an antigen is available.

Rabbit pox virus (myxomatosis): The infection is not likely to be found in well-managed laboratory colonies as the natural mode of transmission is by insects. Diagnosis can be easily made by clinical signs and by post-mortem examination.

Rabbit rotavirus: Infection is non-persistent. Seromonitoring must be carried out using a serogroup A antigen (as in mice).

Rat coronavirus (RCV)/*Sialodacryoadenitis virus* (SDAV): See Coronaviruses.

Rat minute virus (RMV): See Parvoviruses.

Rat parvovirus (RPV): See Parvoviruses.

'*Rat respiratory virus*' (RRV): This is the working name for a novel respiratory pathogen of laboratory rats associated with lymphohistiocytic interstitial pneumonia and perivascular lymphoid cuffing. While initially a viral aetiology was suspected, there is now strong evidence that *Pneumocystis carinii* is an aetiological agent of idiopathic lung lesions consistent with RRV. Clinical signs have not been reported. Diagnosis is based on histopathology and *Pneumocystis*-specific tests such as PCR assays.

Rat theilovirus: See Theiler's murine encephalomyelitis virus.

Reovirus type 3: Besides mice and rats, antibodies have also been found in asymptomatic hamsters, guinea pigs and rabbits, but the virus has not been isolated from any of these species.

Sendai virus: Rodents (mice, rats) are the natural hosts for this virus. Seropositives among other species (including humans) are likely to be due to closely related, serologically cross-reacting viruses (e.g. other paramyxoviruses). Since transmission via dirty bedding is not reliable, the use of cage contact sentinels is recommended.

Theiler's murine encephalomyelitis virus (TMEV): Positive serological reactions in rats are due to a Theiler-like virus ('rat theilovirus'). Positive findings have also been reported in guinea pigs suffering from lameness.

Toolan's H-1 virus: See Parvoviruses.

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Note: The following lists are not all inclusive, only selected papers published during the last 10 years have been included, with a few exceptions.

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Appendix 2: Calculation of the number of animals to be monitored ('ILAR formula')*.

Assumptions (rarely met)

1. Population size > 100 animals
2. Random sampling
3. Random distribution of infection†

Formula

$$\frac{\log(1 - \text{desired confidence level})}{\log(1 - \text{assumed prevalence rate})} = \text{No. of animals to be monitored}^{\S}$$

Number of animals required to detect an infection

	Sample sizes at different confidence levels		
Assumed prevalence rate (%)	95%	99%	99.9%
10	29	44	66
20	14	21	31
30	9	13	20
40	6	10	14
50	5	7	10

Example: Nine animals should be monitored to be 95% confident of finding at least one positive animal if the suspected prevalence rate of an infection is >30%.

*ILAR Committee on Long-Term Holding of Laboratory Rodents. Long-term holding of laboratory rodents. *ILAR News* 1976; 19: L1–25.
†Since the distribution of an infection may be dependent on sex and age, attention should be given to sampling animals of both sexes and of different ages. Similarly, susceptibility to infection and serological response may vary according to differences in strain or breed. Therefore, if more than one strain of a species is present, as many as possible or even all strains may need to be screened, or the sampling rotated between strains over time.
§It should be noted that this equation is simplified. When using the term prevalence it is assumed that this is the real prevalence, which means the number of animals actually infected with the organism. The prevalence to be used for calculation of the sample size, however, is only that fraction out of the real prevalence which will also react positively in the test, and thus depends on the sensitivity of the diagnostic test used. For more information about the correlation between sample size and expected prevalence, the reader is referred to the following reference: Hansen AK. Strategies for sampling animals for bacteriological examination. In: *Handbook of laboratory animal bacteriology*. Boca Raton: CRC Press, 2000, pp. 1–14.

Appendix 3: Example of a health monitoring programme description

Health monitoring programme of the Central Animal Facility

Overview

The Central Animal Facility is composed of 12 animal houses (each comprised of several microbiological units). Nine of them are under barrier and are used for breeding and non-infectious experiments. The other three are dedicated to infectious experiments (Biosafety Levels 2 and 3 [BSL2 and BSL3]).

Except in the BSL2 and BSL3 animal houses, health monitoring has been performed since 1996 for mice and since 2009 for rats (~1000 sentinel mice and ~20 sentinel rats analysed per year). This activity is organized and performed in-house.

The schedule and results of the health monitoring programme are available on the Central Animal Facility website.

The health monitoring programme of the Central Animal Facility is designed to determine and monitor the health status of the animals and to prevent the introduction of interfering microorganisms (pathogens and opportunists). The health status is usually requested by other research laboratories that want to import animals from the Central Animal Facility.

Only animals purchased from approved vendors may be introduced directly into the animal houses. Animals of other origins must be either quarantined or rederived via embryo transfer. The decisions to quarantine or embryo transfer are made by the veterinary staff of the Central Animal Facility, on the basis of the health monitoring report and additional information provided by the animal house of origin and on the projected use of the animals at the Central Animal Facility.

To prevent the spreading of potential contaminants, it is forbidden to transfer:

- animals from one animal house to another animal house;
- animals from one room to another room of the same animal house.

Transfers are allowed in some specific conditions (e.g. after quarantine, animals from microbiologically defined breeding unit). In other cases, permission must be obtained from the veterinary staff and their instructions must be strictly followed.

Basic hygiene rules when handling animals

Microbiological contamination can perturb and/or alter scientific results. Here are the preventive measures that need to be followed to avoid such contamination in any of the animal houses:

- wearing of dedicated facility clothes: head bonnet, covershoes, gloves, disposable gown, blouse;
- sterilization of material and consumables introduced into the animal house;
- decontamination of material taken out of the animal house;
- work hygiene: use of forceps to handle animals, decontamination of the working area before and after working sessions;
- proper elimination of waste;
- only one animal house may be visited on a single day.

As in laboratories, eating, drinking and smoking are strictly forbidden in animal houses.

Animal importation

Microbiological contaminants can enter the facilities through uncontrolled animal importation. This is also true when importing biological material originating from animals (e.g. ascites, organs, cells, antibodies).

Therefore, the introduction of animals and biological materials into the animal houses must follow strict rules.

Approved vendors

Animals of known microbiological quality purchased from vendors approved by the Central Animal Facility are produced according to high standards (i.e. strict breeding procedures, frequent health monitoring) and are allowed to enter directly into the animal houses without any quarantine. Information on these vendors is available on this website.

Other origins

For other origins than the approved vendors an importation request form (see page 38) must be filled out and sent to the Central Animal Facility. The procedure is available on this website.

Depending on the results of the health monitoring of the facility where the animals are coming from, the kind of experiment and the animal house concerned in the recipient facility, the veterinary staff from the recipient facility will decide if the animals will be:

- housed in an isolator for the time of the experiment (short-term experiment);
- introduced directly into the animal house;
- quarantined;
- rederived in order to recover an appropriate health status.

A researcher who wants to import animals from an external institution must wait for the instructions from the Central Animal Facility before contacting the Import–Export service. The Import–Export service will organize the transfer and the reception of the animals.

Quarantine

Quarantine is performed when the animals are likely to be of appropriate health status according to the health information provided by the animal house of origin. Quarantine is a shorter procedure (at least 6 weeks) than rederivation (at least 15 weeks). During quarantine, animals are placed in an isolator which will protect both their health status and confine any unknown contaminant the animals might carry.

The quarantine is organized by the animal facility staff, as follows:

- reception of the animals when they arrive at the Central Animal Facility;
- housing in dedicated isolators;
- contact with sentinel animals for at least 6 weeks;
- health monitoring on the sentinel animals;
- delivery of the animals to the researcher after the quarantine period if their health status is appropriate;
- rederivation of the animals if their health status is not appropriate.

Rederivation (mice)

Embryo transfer can be performed at the Central Animal Facility. To restore an appropriate health status, embryo transfer is performed instead of

hysterectomy because some pathogens are able to cross the placental barrier (e.g. MHV, LCMV, Sendai virus, polyomavirus, MVM).

Animal transfer within the Central Animal Facility

The only authorized transfers within the Central Animal Facility are:

- breeding facility of the Central Animal Facility → experimental facility;
- breeding rooms of the Transgenesis centre → experimental facility;
- non-BSL2 or BSL3 animal facilities of the Central Animal Facility → isolators.

To avoid contamination, no other kind of transfer is allowed between animal facilities or between rooms of the same animal facility. Under certain circumstances (e.g. after quarantine), the veterinarians of the Central Animal Facility can allow transfers after appropriate controls. Veterinarians of the Central Animal Facility must be contacted at———

Use of biological material of animal origin

Veterinarians of the Central Animal Facility must be contacted at——— before using any biological material that originates from animals.

Health monitoring programme

Routine health monitoring concerns all animal facilities' rooms, except BSL2 and BSL3 facilities. Focused health monitoring can be conducted on animal colonies bred in isolators or on sick animals.

Health monitoring can be conducted either on experimental animals or on sentinels. Sentinels used are immunocompetent outbred animals of known health status and kept at least 10 weeks under conditions promoting their contamination by other animals.

Sentinels are used for the health monitoring of all facilities at the Central Animal Facility. They are exposed to samples from soiled cages of experimental animals (bedding, bottle, cage lid) every week. The location of the soiled cages used for sentinels' exposure is planned and recorded every week. Cages in the rooms are sampled for 10 to 12 weeks.

In the breeding facility managed by the Central Animal Facility, health monitoring is performed on retired breeders of each strain exposed to soiled cages.

Health monitoring in the Central Animal Facilities includes two screening programmes:

- full screening comprises ectoparasites, endoparasites, digestive and respiratory bacteria and extensive rodent specific viruses;
- reduced screening comprises ectoparasites, endoparasites and the most prevalent rodent viruses. This reduced list of viruses is established following FELASA recommendations.

There is at least one full screening per year for each facility. The health monitoring plan is available on this website.

Animal exports

Exports of animals to laboratories outside the Central Facility are common practice. In most cases a health report is requested by the recipient, showing the detailed health status of the animal facility of origin. The results of health monitoring of the originating animal facility are available from the Central Animal Facility website.

Once the veterinarian of the recipient animal facility has given formal approval for the acceptance of the animals, the Import–Export service will organize the shipment. The Central Animal Facility provides appropriate shipping boxes and water gel. The detailed procedure for shipping of live animals is available from the Central Animal Facility website.

The day the animals are shipped, a veterinarian of the Central Animal Facility checks the animals and transport box and delivers the necessary health certificate.

If a pathogen is detected

If a pathogen is detected there are three options:

- if the presence of the microorganism is considered acceptable (i.e. with reduced or no impact on scientific results), its presence may just be acknowledged without any other action; it is however preferable to take measures that will limit its dissemination to other animal rooms and other animal facilities;
- when an efficient treatment is available (e.g. for pinworms), animals may be treated to eradicate the infection;
- when a major pathogen is found and no treatment is available, the infected colonies will be killed and replaced by animals of appropriate health status (e.g. purchase of new animals) in the animal room after it has been cleaned and disinfected appropriately.

– RECIPIENT ANIMAL FACILITY –

ANIMAL HEALTH INFORMATION

The aim of this form is to collect information on the animal facility and on the colony from which mice to be imported to the recipient animal facility originate. Please, fill this form as accurately as possible and provide all relevant information that will help veterinarians to take appropriate decisions before reception of the mice.

CONSIGNEE AT THE RECIPIENT FACILITY:

Last Name: _____ Unit: _____

ORIGINATING INSTITUTION:

Investigator last name: _____ First: _____

Vivarium: _____ Vivarium room: _____

Veterinarian last name: _____ First: _____

Vet phone: _____ Fax: _____ Email: _____

Additional contact(s): _____

COLONY DESCRIPTION: Approximately colony size: _____

Immune status: ☐ Normal ☐ Deficient ☐ Undetermined

Breeding in room?: ☐ YES ☐ NO

Colony status: ☐ Closed ☐ Open ☐ Open with quarantine required

Animals in room belong to: ☐ A single research group ☐ Multiple research groups

Do incoming animals come from multiple sources?: ☐ YES ☐ NO

Can rodents be returned to room after removal?: ☐ YES ☐ NO

SENTINEL PROGRAMME:

Mouse boxes in room: ___ # Sentinel boxes in room: ___ # Mice per sentinel box: ___

Sentinel on dirty bedding?: ☐ YES ☐ NO If no, give details:_____

Frequency of monitoring: ☐ Monthly ☐ Quarterly ☐ Semi-annually ☐ Annually

Diagnostic tests performed: ☐ Ectoparasites ☐ Endoparasites ☐ Bacteriology ☐ Viral serology

List pathogens or other health problem in room: _____

List pathogens or potential pathogens present in other rodent rooms in same vivaria: _____

☐ No pathogen present in any rodent room

Attach the two most recent health monitoring reports. Each report should clearly mention the rodent rooms from which the mice examined originate.

HUSBANDRY:

Is husbandry shared with any rooms that contain potential rodent pathogens?: ☐ YES ☐ NO

If yes, list pathogens: _____

Caging system: ☐ Conventional ☐ Filter-topped cages ☐ Individually ventilated cages ☐ Other: _____

Protective equipment: ☐ Gloves ☐ Shoe cover ☐ Disposable clothing ☐ Mask ☐ Shower in ☐ Change hoods

Please fax back to the Veterinary Office (number below)

For any questions, **Email:** _____ **Fax:** _____

Veterinarian: _____

(Printed name) (Signature) (Date)