Rabies

Control Tools

Diagnostics availability

Commercial diagnostic kits available worldwide

Rapid immunochromatographic test kits provide a simple and rapid method for rabies detection. They need neither cold chain for transportation nor complicated training for personnel. This diagnostic test is suitable for rabies screening, particularly in areas with a high prevalence of rabies and where the fluorescent antibody test is not available.

Real time PCR kits for use on different platforms such as ABI, *Smart Cycler, *Opticon, *I Cycler, *Mx 3005P, etc.

GAP: Training for dRIT for laboratory personnel in resource poor countries would provide more access to diagnostic capability. Real time PCR in national laboratories could help to elucidate the epidemiology of rabies.

Commercial diagnostic kits available in Europe

As 15.1

Diagnostic kits validated by International, European or National Standards

Platelia Rabies II ELISA for the determination of immune status post-vaccination in individual dogs or cats (for regulation of international movement or trade), and in fox populations (for monitoring wildlife vaccination programmes on the OIE list

GAP: Continuing educational training on the kit for professional laboratories. Improved quality assurance programs need to be put in place.

Diagnostic method(s) described by International, European or National standards

Identification of the agent: Agent identification is preferably done using the fluorescent antibody test (FAT) which provides a reliable diagnosis in 98–100% of cases for all serotypes if a potent conjugate is used. For a large number of samples, as in an epidemiological survey, polymerase chain reaction (PCR) or immunoenzyme techniques can provide rapid results.

Identification of post-vaccinal antibodies: Virus neutralisation (VN) assays in cell cultures are the prescribed tests for international trade. Alternatively, use may be made of a test that is known to correlate with these, notably an enzyme-linked immunosorbent assay using antibody to the G protein. Results are expressed in International Units or equivalent units relative to an international standard antiserum

GAP: Developing a strategy for ‘screening’ using ELISA kits and then for doing VN assays for only a further selected number of serological samples could reduce costs for post vaccination monitoring. If this was implemented as a strategy to reduce time and costs of testing, collaboration will be required to establish ‘cut-off’ titres etc.

Commercial potential for diagnostic kits in Europe

Limited

GAP: There maybe a market for developing a dRIT tests for resource poor countries.
**Vaccines availability**

**Commercial vaccines availability (globally)**

A wide range of vaccines authorised globally. There are human, cat, ferret, horse, sheep, cattle, and dog rabies vaccines.

All vaccines currently used for oral vaccination programmes are either modified live-virus vaccines or live recombinant vaccines.

**GAP:** There is a need for longer lasting (perhaps lifelong) rabies vaccines. Additionally, a combination rabies vaccine and contraceptive would provide a valuable tool in the fight against rabies.

**Commercial vaccines authorised in Europe**

A range of vaccines are authorised in Europe. Inactivated rabies virus vaccines are licensed for use in cats and dogs.

**Marker vaccines available worldwide**

None

**Marker vaccines authorised in Europe**

None

**Effectiveness of vaccines / Main shortcomings of current vaccines**

1 Vaccination is the favoured method of control of rabies in reservoir populations of dogs and wildlife. The development of oral vaccines has enabled the eradication of rabies from the red fox population throughout most of Europe. In addition, programmes for oral vaccination of wildlife such as raccoons, coyotes, foxes, and skunks are being undertaken in North America animals using oral baits in areas where rabid wildlife are frequently found. For oral vaccination, either attenuated rabies strains or live-recombinant vaccines may be used. The vaccine should not induce any adverse signs in target and non target species

2 For animals, live and recombinant vaccines are effective by the oral route and can be distributed in baits in order to immunise wild (or domestic) animals. Different standards apply to vaccines containing live virus modified by passage in eggs or cell cultures to reduce its virulence for the target animal, and to vaccines prepared from inactivated virus.

3 Both types of vaccine have their advantages and disadvantages, but they can both be used to immunise animals for periods of between 1 and 3 years. Live attenuated rabies vaccines are not accepted in some countries.

4 Recombinant vaccines (e.g. vaccinia rabies-glycoprotein recombinant) have also proved to be effective. These are not live rabies vaccines as they are prepared by inserting non-infectious rabies nucleic acid into a vector such as vaccinia or canary pox

5 In S.America losses in cattle can be attributed to inadequate use of the vaccines, and to failure of the vaccine to adequately immunize the animals or to protect them against possible antigenic variations of the rabies viruses present in the bat populations.

**Commercial potential for vaccines in Europe**

Commercial potential exists in endemic countries but it is unlikely there will be any increased market in Western Europe although the situation in eastern Europe may necessitate increased demand for vaccination...

**Regulatory and/or policy challenges to approval**

Recombinant vaccines may not be acceptable in some countries
GAP: Need to consult with and lobby regulatory authorities regarding contraceptive vaccine for dogs.

**Commercial feasibility (e.g. manufacturing)**
Feasible

**Opportunity for barrier protection**
Vaccination could be used for barrier protection around outbreaks in new regions.

**Opportunity for new developments**
WHO stimulated studies on oral vaccination of dogs (OVD) and the development of safer and effective vaccines and baits for OVD. OVD offers new approaches promising a significant increase in the dog vaccination coverage (especially of free-roaming and poorly supervised dogs) both when applied exclusively or in combination with parenteral vaccination. A number of requirements regarding safety of candidate vaccines and safety, efficacy and economics of bait delivery (using placebo baits) still remain to be fulfilled. WHO-coordinated laboratory and field research on OVD carried out over the years has however been fruitful and created the proper conditions for launching field trials in places where dog accessibility to parenteral vaccination has been identified as the obstacle to rabies elimination.

GAP:
Oral or parenteral contraceptive vaccine for dogs, in combination with rabies vaccines may be a valuable option. Longer lasting rabies vaccines – perhaps even lifelong immunity.

**Pharmaceutical availability**

**Current therapy (curative and preventive)**
Antiviral agents, interferon and massive doses of rabies immunoglobulin have been used to treat human cases, but seem only to prolong the clinical course without affecting fatality.

GAP: There have been two human rabies survival cases in the US as reported recently. More research into modifying treatments and determining the most effective anti-virals is needed.

**Future therapy**
Unlikely in animals

**Commercial potential for pharmaceuticals in Europe**
Limited

GAP: Development of an appropriate animal model that could be used to improve human treatment regimens.

**Regulatory and/or policy challenges to approval**
No issues

**Commercial feasibility (e.g. manufacturing)**
None
Opportunities for new developments

None at present

New developments for diagnostic tests

Requirements for diagnostics development

The identification of the agent can be supplemented in specialised laboratories by identifying any variant virus strains through the use of monoclonal antibodies, specific nucleic acid probes, or the PCR followed by DNA sequencing of genomic areas. Such techniques can distinguish between field and vaccine strains, and possibly identify the geographical origin of the field strains. These very sensitive tests should be used by well trained personnel in specialised laboratories.

GAP: Establishment of SOPs that would provide listing of all antibody panels that could potentially be available to all laboratories.

Time to develop new or improved diagnostics

In general the time for development of new tests depend on the nature of the test. The transfer of a new test form the research phase to a diagnostic tool which is commercially available will take time possibly several years.

Cost of developing new or improved diagnostics and their validation

Developing new tests will be costly but the validation of new tests will be both time and labour intensive which in turn will be costly.

GAP:

dRIT is already established and what is needed is to have a ‘pilot study’ of the dRIT in a resource poor country to prove that it would be a useful new tool for diagnostics and surveillance.

Lateral Flow Devices (LFD) have been developed and are commercially available, however, their sensitivity and specificity is yet to be questioned. What is needed here is a comparative study on commercially available LFDs using a selected panel of representative lyssaviruses from across the world.

Research requirements for new or improved diagnostics

Develop tests to identify incubating animals. Tests to identify infection in live animals if considered to be carriers

Technology to determine virus freedom in animals

Freedom of virus in animals is impossible to determine at present due to the lack of host antibody response and the restriction of the virus to the neural tissues and salivary gland.

GAP: There is currently no diagnostic test to identify rabies infection prior to an animal showing clinical signs.

New developments for vaccines

Requirements for vaccines development / main characteristics for improved vaccines

Current vaccines are effective and give a solid immunity. Before newly developed vaccines can be licensed, the duration of immunity resulting from their use should be determined in vaccinated animals of the target species. Vaccines should confer protective immunity for at least 1 year. For live virus vaccines, the minimum virus content that will elicit an adequate immune response must be established. For live vaccines that are prepared for oral vaccination of wild (or domestic) animals, safety and efficacy in target animals and safety in non target species must be demonstrated.
The development of combination vaccines to include a rabies element as well as other diseases has some merit and such vaccines are in production.

GAP:

New vaccines for lyssaviruses not covered by current vaccines. Longer lasting vaccines that could provide lifelong protection to animals.

Need to develop universally accepted criteria for vaccine potency testing. The current in vivo assay (NIH) requires the use of >70,000 mice annually. The test is highly variable and urgently needs to be replaced by a combination of in-vitro testing (e.g. Trimeric glycoprotein quantification) and consistency monitoring.

**Time to develop new or improved vaccines**
A long period of 5-10 years is always anticipated for development of new vaccines

**Cost of developing new or improved vaccines and their validation**
Very expensive and little probability of a much larger market in Europe

GAP: Production of a vaccine bank that could provide the vaccines to nations that require them and are willing to establish a canine rabies prevention program.

**Research requirements for new or improved vaccines**
- Further research should be undertaken on use of oral vaccines for domestic species especially in inaccessible dogs.
- Research aimed at development of new biological tools should be encouraged i.e. specific contraceptive vaccines for reservoir species.
- There is a critical need for establishment of an oral vaccine bank for emergency use.
- Need exists for development of oral vaccines/baits/delivery systems for use in all terrestrial animals.
- Recombinant (live vector) vaccines for parenteral vaccination of domestic immuno-stimulating genes to make the vaccines more potent. Animals could be considered for rabies control purposes as an alternative to inactivated vaccines.
- Research into disease dynamics, vaccines and effective delivery mechanisms for target populations
- Develop recombinant vaccines which incorporate immuno-stimulating genes to make the vaccines more potent.

GAP:
Need to improve financial support to develop these new vaccines and perhaps to provide tech transfer to countries that could produce the vaccines themselves.

**New developments for pharmaceuticals**

**Requirements for pharmaceuticals development**
None

**Time to develop new or improved pharmaceuticals**
Not applicable

**Cost of developing new or improved pharmaceuticals and their validation**
Not applicable

**Research requirements for new or improved pharmaceuticals**
Not applicable
Disease details

Description and characteristics.

Pathogen

Rabies is caused by 12 species of neurotropic viruses in the genus Lyssavirus, family Rhabdoviridae. Two newly identified lyssaviruses (Bokeloh Bat Lyssavirus, Germany 2010 and Ikoma Virus, civet, Tanzania 2011) are yet to be accepted by ICTV. The latter is highly divergent.

GAP: Lack of comprehension of the complete pathogenesis of disease; new viruses that are not covered by current vaccines.

Variability of the disease

There are several strains of the classic rabies virus (RABV) with each strain generally maintained in particular reservoir host(s).

The negative sense RNA genome encodes a small leader sequence followed by the N (nucleocapsid), P, M (membrane), G (envelope glycoprotein) and L (replicase) proteins which are translated from five capped and polyadenylated monocistronic mRNAs, each encoding one of the five viral proteins.

GAP: Lack of data on variability of disease in various species, ie why some animals are more inclined to exhibit furious vs paralytic rabies; lack of epidemiological data on new and existing lyssaviruses; lack of research on why some animals shed virus for longer periods of time and why some animals may survive the disease while others succumb.

Stability of the agent/pathogen in the environment

Lyssaviruses can be inactivated by lipid solvents (soap solutions, ether, chloroform, acetone), 1% sodium hypochlorite, 2% glutaraldehyde, 45-75% ethanol, iodine preparations, quaternary ammonium compounds, formaldehyde or a low pH. This virus is also susceptible to ultraviolet radiation or heat of 1 hour at 50° C. It is rapidly inactivated in sunlight, and does not survive for long periods in the environment except in a cool dark area.

GAP: Lack of data on the efficacy of various substances used to eliminate or degrade virus after a bite wound. What is the value of ‘washing the wound’? Can washing the wound with specific substances improve survivability after a bite exposure if the patient cannot receive RIG or travel time to get PEP is extended?

Species involved

Animal infected/carrier/disease

Lyssaviruses are transmissible to all mammals. The animal hosts that maintain rabies virus in nature are carnivores and viverrides (RABV) and bats (RABV and most other lyssaviruses). Other animals do not play a role in the maintenance of the disease, but are victims of the disease.

GAP: What bat species are involved? Why does there appear to be a species barrier for some bat lyssaviruses? – Why are there limited spill over infections even when bats co-roost with other species of bat or animal? Are specific receptor molecule or virus load threshold involved? Identification of new lyssaviruses. Rabies virus can mutate to be better adapted to a new animal species (Dog to fox in Europe, bats to skunks in Arizona for example); more research on why does this occur is needed.

Human infected/disease

Lyssaviruses are transmissible to humans by inoculation. Inhalation of rabies virus is an extremely rare event. Human cases
have occurred in US and Germany via transplantation of infected organs from an undiagnosed donor. The disease is fatal to humans.

GAP: Why do some humans and bats survive after exposure without contracting the disease (some humans and bats have been reported to have antibody titers without having been vaccinated)?

**Vector cyclical/non-cyclical**

Important animal vectors include the dog, cat, vampire bat, mongoose, skunk, wolf, raccoon, and fox.

GAP: What causes rabies to adapt to a new vector species?

**Reservoir (animal, environmental)**

Reservoir hosts for RABV important in various world regions include: insectivorous bats, skunks, raccoons and foxes in the U.S.; foxes in continental Europe, Canada, Greenland and the former Soviet Union; Dogs in Africa, Asia, and Central and South America; jackals in parts of Africa, Asia and the Middle East; vampire bats in South America; mongooses in the Caribbean; meerkats in southern Africa; raccoon dogs in Eastern Europe and the Far East. Generally, bats serve as reservoirs for most of the lyssaviruses. All but two lyssaviruses (Mokola and Ikoma) have been identified in bats.

GAP: The epidemiology of various animal species is not well documented. The dog and cat population estimates and animal movements are poorly understood worldwide. Even UK and US population estimates are arbitrary due to a lack of an enforced registration system. Although the UK has some data for movements with the continent (PET Travel Scheme), there is little data on inter-continental movements.

**Description of infection & disease in natural hosts**

**Transmissibility**

Infection is usually spread by the bite of an infected animal because the virus is present in the saliva. The virus is shed intermittently in saliva. Little is known about the quantity of a particular virus in the saliva which would effect a successful exposure (threshold or specificity)? Very little quantitative analysis is performed on human or animal saliva during or prior to the clinical phase of the disease.

GAP: Understanding the difference in transmissibility of various rabies virus variants and animal species.

**Pathogenic life cycle stages**

Not applicable.

**Signs/Morbidity**

Clinical signs of rabies in animals are well documented. At first, affected animals show changes in their behaviour. Typical signs include sudden behavioural changes and progressive paralysis leading to death. In some cases, however, an animal may die rapidly without demonstrating significant clinical signs.

GAP: Documenting clinical signs as related to the pathogenesis of the virus as it travels along the nervous system to the brain and back to the body organs.

**Incubation period**

The incubation period varies with the amount of virus transmitted, virus strain, site of inoculation (bites closer to the head have
a shorter incubation period), host immunity and nature of the wound. In dogs and cats, the incubation period is 10 days to six months; most cases become apparent between two weeks and two months. In bats the incubation period can even be longer.

**Mortality**

Once symptoms appear, rabies is always fatal in terrestrial animals.

**GAP:** What is the specific correlation between the incubation period and site of bite; is there a difference in length of incubation period and virus variant

**Shedding kinetic patterns**

As well as affecting the central nervous system, rabies virus can also colonise the salivary glands which allows the transmission of infection by infected saliva through bite wounds – the usual route. Animals may excrete virus by this route before the development of clinical signs, for up to 13 days in dogs. Duration of virus excretion before the onset of clinical signs differs among animals.

**GAP:** Investigation into the difference in shedding period according to the virus variant and animal dependent upon an understanding of the infective dose of native virus in saliva required to initiate an infection which mimics a field case. Experimental studies species involved. Such investigations are highly are hampered by the need to amplify strains in tissue culture to ensure sufficient standardised volume to inoculate a statistically significant number of animals. The virus may thus be attenuated and inoculated at sub-optimum levels to reflect a natural exposure.

**Mechanism of pathogenicity**

The virus will generally remain at the entry site for a period of time before travelling along the nerves to the brain. In the brain, the virus multiplies quickly, resulting in clinical signs. The virus then moves from the brain along nerves to the salivary glands (and other peripheral organs).

**GAP:** Why does the virus sometimes stay in an ‘eclipse’ phase for weeks, months or even years? Better understanding could help to understand the pathogenesis and better treatment after infection

**Zoonotic potential**

**Reported incidence in humans**

Rabies is widely distributed across the globe. More than 55,000 people die of rabies each year. About 95% of human deaths occur in Asia and Africa. Most human deaths follow a bite from an infected dog. Between 30% to 60% of the victims of dog bites are children under the age of 15.

**GAP:** There is no accurate surveillance system for the number of rabies deaths globally. Most go unreported. A more accurate survey is currently underway by the PRP but needs support. New models need to be developed on incidence of disease

**Estimated level of under-reporting in humans**

In developed countries, widespread vaccination and animal control programmes have reduced the incidence of the disease in
man to low levels. Human cases are now rare in Europe. African and Asian countries are particularly affected by rabies because the virus is maintained there in animal reservoirs and there is often inadequate healthcare and lack of control measures.

GAP: Better assessment is needed on the risk of rabies in humans as related to lack of access to vaccines due to cost, travel time, unavailability of RIG etc.

**Risk of occurrence in humans, populations at risk, specific risk factors**

Once the signs and symptoms of rabies start to appear, there is no treatment and the disease is almost always fatal.

GAP: Two recent human treatment successes after treatment using the ‘Milwaukee’ protocol indicate that in some cases, humans can be saved after contracting rabies. More research is needed to better determine the most effective treatment protocols.

**Symptoms described in humans**

The true disease burden of rabies is largely under-estimated, especially in Africa due to poor surveillance, reporting and investigation. Under reporting of rabies is likely because many countries lack the necessary diagnostic facilities. Also the populations most affected tend to be rural (especially in developing countries) with erratic surveillance.

GAP: Up to 10.5% of deaths in children originally reported to be caused by cerebral malaria in Malawi were actually infected with rabies. Better data collection is needed. The use of the less expensive dRIT would be most useful in helping to provide better diagnostic tests for developing nations. There is a need for training on dRIT and implementation of newer surveillance tools, like mobile phone technology.

**Likelihood of spread in humans**

Dogs continue to be the main carrier of rabies in Africa and Asia and are responsible for most of the human rabies deaths worldwide. Humans most often become infected with rabies through the bite or scratch of an infected dog or cat.

GAP: One of the biggest gaps is an effective contraceptive to control the dog population, the main animal causing human exposure and death. Culling alone has been shown to be ineffective in reducing the population and disease prevalence. By effectively and humanely reducing the dog population, a number of public health issues could be resolved, or at least reduced.

**Impact on animal welfare and biodiversity**

**Both disease and prevention/control measures related**

The disease is distressing for the affected animals. Attacks by rabid carnivores compromise the welfare of other animals.

GAP: A humane and effective dog contraceptive would significantly help to reduce the dog population and thus the interaction between dogs and humans as well as dogs and other animals. Additionally, increased and improved educational programs that are culturally sensitive and effective and that focus on animal welfare and rabies prevention need to be established and disseminated. One study in the Philippines has shown that by increasing educational awareness about responsible pet ownership, dog bites in children were reduced by up to 50% within the first year. This improves the relationship between animals and humans thus having a direct impact on animal welfare.

**Endangered wild species affected or not (estimation for Europe / worldwide)**
Outbreaks of rabies in susceptible wild species can have a major impact on populations, e.g. the Ethiopian wolf.

GAP: Decreasing the exposure rate between wild life species and rabies vectors is essential and understanding the efficacy of rabies vaccines in wildlife species is critical, including whether the vaccine is safe to use in endangered species.

Slaughter necessity according to EU rules or other regions

Affected animals will die. Early slaughter of individuals may be necessary for diagnosis and to alleviate pain and suffering.

GAP: The use of dogs and other animals as food sources is not widely understood but exposure may occur during preparation of the carcase. We do not know enough about how widespread this is in many resource poor countries and what the incidence of rabies is in dogs taken to market to be sold for meat.

Geographical distribution and spread

Current occurrence/distribution

Rabies is widely distributed throughout the world and is present in all continents. The number and size of rabies-free countries, territories, or areas are small compared to those of rabies-affected areas. According to the WHO rabies database RabNet in 2005, 43 out of 129 countries and territories, which provided data, reported no rabies for that year and had no rabies cases in 2004. Many rabies-free countries and territories are islands of the developed world (e.g., Japan, New Zealand) and the developing world (e.g., Barbados, Fiji, Maldives, and Seychelles). In addition, large parts of western and central Europe and Latin America (e.g., Uruguay and Chile) are also free of rabies.

GAP:

There is a gap on data reflecting the true incidence of rabies and the economic burden globally. The PRP is currently working on a study to help evaluate the global burden but partners are needed to complete the study and evaluate the impact of disease burden and various models that could provide an economic evaluation of interventions.

Epizootic/endemic - if epidemic frequency of outbreaks

Rabies is maintained in two epidemiological cycles, the urban and sylvatic cycles. In the urban rabies cycle, dogs are the main reservoir host. This cycle is predominant in much of Africa, Asia, and Central and South America, where the proportion of unvaccinated and semi-owned or stray dogs is high. The sylvatic (or wildlife) cycle is the predominant cycle in Europe and North America. It is also present simultaneously with the urban cycle in some parts of the world. The epidemiology of this cycle is complex; factors affecting it include the virus strain, behaviour of the host species, ecology and environmental factors.

A third cycle is linked to various species of either haematophagous, frugivorous or insectivorous bats.

GAP: More data are needed on the lowest incidence of vaccination coverage required to be effective as it relates to population data.

Seasonal cycle (seasonality)

None

GAP:

Is there a seasonality in bats or other species? More needs to be understood about the disease mechanisms which allow the virus to be maintained for long periods during hibernation e.g. bats, raccoon dogs etc.
**Speed of spatial spread during an outbreak**

Variable and depends on the distribution of the hosts and susceptible species

GAP: Models need to be developed on the spatial spread of rabies in an outbreak situation. This would help to provide a cost estimate on how to halt the spread as well as strategic plans for implementation.

**Transboundary potential of the disease**

In free countries the main risk is the importation if infected animals Rabid animals imported from enzootic areas are reported every year in rabies-free areas. These importations threaten the rabies-free status of terrestrial animals in western European countries and challenge the public health surveillance system and the health structures. Where wildlife hosts exist the potential for spread is high if the reservoir species move freely across boundaries. Recent outbreaks in Indonesian islands seem to be linked with the transportation of infected dogs via fishing boats.

GAP: More research is needed on how to develop regional plans on development of effective rabies prevention on a large scale and how to more effectively provide monitoring systems to prevent rabies from re-entering, what to do if and when it is reintroduced.

**Seasonal cycle linked to climate**

No but there is anecdotal evidence that climate change can effect the rodent populations in Northern Europe which in turn can effect the populations of rodent eating arctic foxes.

GAP: Further data is required to understand the effect on rabies cycles within species effected either directly or indirectly by climate change/seasonality.

**Distribution of disease or vector linked to climate**

No

**Outbreaks linked to extreme weather**

No

**Sensitivity of disease or vectors to the effects of climate change (environmental changes/land use)**

No

GAP: Vampire bats, the main vector of rabies in cattle in L America, are moving north in N America as temperatures rise.

**Route of Transmission**

**Usual mode of transmission (introduction, means of spread)**

This virus is usually transmitted in the saliva of an infected animal. Infection occurs primarily via bite wounds or infectious saliva entering an open cut or wound. Less often, it is spread by infection entering mucous membrane, such as those in the mouth, nasal cavity or eyes. The rabies virus is not transmitted through intact skin.

GAP: There are gaps in understanding the transmission rate of specific rabies viral variants and whether specific variants
replicate faster than others in epithelial cells, thus making transmission more of a risk factor

**Occasional mode of transmission**

There are rare reports of transmission by other routes. A few cases have been reported after corneal transplantation and a single organ donor in the U.S. infected three recipients of kidney or liver transplants. Aerosol transmission has been documented in special circumstances for example, in the environment of a densely populated bat cave. There is also some speculation that ingestion could play a role in wild animals although exposure is more likely to occur during eating rather than digestion (gastric juices likely to kill virus). There has been some evidence for transmission of virus from saliva via abrasions in the mouth of kudu as they feed on thorny acacia trees.

GAP: Research into better and easier diagnostic tests that are developed for organs being transplanted. Research on the ingestion route as a means of transmission needs to be investigated as it could play a role in maintaining rabies in an area.

**Conditions that favour spread**

Dense population density of reservoir hosts and susceptible species. Poor controls and lack of vaccination of dogs.

GAP: The population density and transmission of rabies needs further investigation as it relates to vector species.

**Detection and Immune response to infection**

**Mechanism of host response**

Pathological changes in the brain. Limited immunological response.

GAP: There are gaps in understanding how to stimulate a more effective immunological response to rabies as it is transmitted along the nerves after exposure.

**Immunological basis of diagnosis**

Antibodies against the virus are rarely useful for the diagnosis of clinical cases, as the host usually dies before developing antibodies. However, the detection of antibodies in a previously unvaccinated host is predictive.

GAP: Assays need to be developed for earlier diagnosis of rabies in humans. This could provide more time to save lives through treatment and by preventing further exposures.

**Main means of prevention, detection and control**

**Sanitary measures**

In free countries the strategy is to prevent the introduction of the disease by the application of import controls, quarantine and post import checks. A rabies contingency plan to stamp out the disease if it occurs should be in place. Depending on the circumstances this could involve controls on domestic pets, vaccination, restrictions on animal gatherings, detention of stray animals and vaccination or destruction of wildlife in limited areas.

In countries where the disease is endemic, measures are implemented to address and reduce the risk of infection in susceptible populations (wildlife, stray and domestic animals) and create a buffer between the animal source of the disease and humans.

- Surveillance and reporting of suspected cases of rabies in animals
- Vaccination programs for domestic animals
- Wildlife rabies control programs including vaccination (trap/vaccinate/release or delivery of oral vaccines)
- Population control and vaccination programs for stray animal populations
In S. America where rabies is a major problem to the cattle industry the only effective means of rabies control in herbivores is routine vaccination and control of the vampire bat (Desmodus rotundus) populations.

**GAP:** Cost benefit analyses need to be developed that would determine the effectiveness and long range financial savings of developing and implementing strategic rabies plans. Looking at the cost savings of rabies in health strategies could be convincing evidence for improving governmental support of prevention programs.

**Mechanical and biological control**

- Quarantine
- Vaccination of domestic dogs
- Stray dog control
- Oral vaccination of stray dogs
- Oral vaccination of foxes

**GAP:** Development of a combination rabies vaccine and dog contraceptive would be a new and effective tool for rabies prevention strategies. Determining the best overall strategy for implementing oral and parenteral rabies vaccination in dogs – when and how to use each strategy. What is the cost effectiveness of reducing the dog population vs not reducing the dog population in concert with rabies vaccination programs.

**Diagnostic tools**

As no clinical sign or gross post-mortem lesion domestic or wild animals, the diagnosis of rabies has to rely on laboratory testing. Rabies is diagnosed using the direct fluorescent antibody (DFA) test, which looks for the presence of rabies virus antigens in brain tissue. The test requires that the animal be euthanized.

**a. Identification of the agent.**

- Histological methods- this test is rarely performed in reference labs. It may still be performed in basic poorly resourced labs (cheap) but it is unreliable.
- Immunological methods-FAT, immunochemical, immunohistochemical, Rapid rabies enzyme immunodiagnosis (RREID)
- Virus isolation
- PCR techniques

**b Antibody detection techniques**

Serological evidence of infection is rarely useful because of late seroconversion and the high mortality rate of host species although such data may be used in some epidemiological surveys. Antibody detection is used as a demonstration of rabies vaccine efficacy.

Modern diagnostic methods, using monoclonal antibodies and molecular techniques, are able to characterise rabies viruses to identify their geographical origin and host species. can be considered pathognomonic in domestic or wild animals, the diagnosis of rabies has to rely on laboratory testing. Rabies is diagnosed using the direct fluorescent antibody (DFA) test, which looks for the presence of rabies virus antigens in brain tissue. The test requires that the animal be euthanized.

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**GAP:** Introduction of dRIT into areas, regions where there is a lack of diagnostic facilities needs to be investigated. There are huge gaps in availability of diagnostic laboratories in resource poor regions of the world. Expensive and labour intensive diagnostic tests are not likely to be the strategy to increase the number of laboratory facilities, new less expensive and even
field tests need to be tested and made available to those that need them.

Gaps in training of personnel in diagnostic laboratories in resource poor countries. Lack of continuing education and ongoing quality assurance programs.

PCR based tests are yet to be ‘recommended’ by WHO/OIE. The benefit of molecular tests is widely understood but the danger of contamination/mishandling in less experienced labs causes concern. Such tests are generally used a confirmatory test and for the added benefit of genetically typing the virus.

**Vaccines**

Rabies vaccines for use in animals contain either
- live virus attenuated for the target species (such as Flury low egg passage, Flury high egg passage, Street-Alabama-Dufferin or Kelev), or
- virus inactivated by chemical or physical means,
- or recombinant vaccines.

The virus is cultivated in embryonated egg, or in cell cultures. Rabies vaccines are usually lyophilised, but inactivated virus vaccines, preferably with an adjuvant, may be stored in liquid form.

GAP: Development of longer lasting rabies vaccines for animals. Replacement of all nervous tissue vaccines with more modern and less reactogenic vaccines.

**Therapeutics**

While treatment of clinically infected animals and man is of no avail, post exposure treatment of man with vaccine and hyperimmune serum is used successfully. This remedial treatment is only partially successful in dogs and other animals and is therefore not recommended.

GAP: There have recently been two human survivors of rabies in the US. Continuing to modify treatment regimens for humans needs to be supported.

**Biosecurity measures effective as a preventive measure**

Humans working with suspect material must be vaccinated against lyssaviruses or other pathogens that may be present in diagnostic samples. The laboratory must comply with national bio containment and biosafety regulations to protect staff from contact with pathogens.

GAP: There are gaps in the number of laboratories that can conduct testing using live rabies viruses. At least one national laboratory in every country for manipulation of rabies virus should be in place.

**Border/trade/movement control sufficient for control**

Based on history, clinical freedom, identification and effective vaccination prior to movement.

GAP: Rabies continues to spread from infected to non-infected areas. More effective border controls needs to be put in place. Education is lacking on the importance of keeping unvaccinated dogs out of rabies free countries.

**Prevention tools**

Prophylactic vaccination of dogs and vaccination campaigns for wildlife reservoirs.
Combination rabies vaccines and dog contraception would help eliminate rabies in regions where dog rabies is present and dog populations are not being controlled at all or except through mass inhumane culling.

**Surveillance**

Notification and reporting of suspect disease with effective laboratory facilities to confirm outbreaks is important to assess the level of the problem.

**Past experiences on success (and failures) of prevention, control, eradication in regions outside Europe**

In many parts of Asia and Africa, the vaccination coverage established in the dog population (30% to 50%) is not high enough to break the transmission cycle of the disease. Where high levels of coverage can be achieved the incidence of rabies in dogs will decline.

A trend toward a decline in the number of cases in animals has been reported in many European countries. Some of these countries are now free of rabies such as Belgium, France, Luxembourg and Switzerland. This improvement followed the massive use of the oral immunization technique for foxes and the dispersal over wide areas since 1989 remarkable decreases have also been noted in Canada and Texas (USA), where oral vaccination projects targeting coyotes and foxes, respectively, have been conducted.

Cooperation between many different ministries needs to be established. Governments need to be supportive if programs are to be sustainable. Thus, programs should be developed in a holistic manner. There is a need to determine what sustainability factors need to be in place to make a program not only successful but sustainable in the future.

**Costs of above measures**

Costs of vaccine and application can be high. Baiting to control rabies in wildlife can be costly.

**Disease information from the OIE**

**Disease notifiable to the OIE**

Listed

**OIE disease card available**

http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/Disease_cards/RABIES-EN.pdf

**OIE Terrestrial Animal Health Code (reference)**

http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.8.10.htm

**OIE Terrestrial Manual (reference)**

http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.01.13_RABIES.pdf

**Socio-economic impact**
Rabies kills at least 55,000 people each year, half of whom are children under the age of 15 even though effective vaccines for post exposure prophylaxis (PEP) are available and over 15 million individuals actually receive rabies PEP each year. Each individual will receive varying numbers of doses of the vaccine and if we presume the same level of underreporting that we see for the disease, the 15m is probably way off too!! It is also believed that the figure is a serious underestimate as there are an estimated 25 million doses of rabies vaccine produced in China alone.

Rabies is primarily a disease of children, who are particularly at risk due to their close contact with dogs. Conclusions drawn are that deaths due to rabies are responsible for 1.74 million disability-adjusted life years (DALYs) lost each year (90% CI=0.75-2.93). An additional 0.04 million DALYs are lost through morbidity and mortality following side-effects of nerve-tissue vaccines.

GAP: Education can save lives and many countries lack culturally sensitive education materials. These figures do not include the global figures.

Zoonosis: cost of treatment and control of the disease in humans

The disease is of significant economic importance in areas where it is endemic. Treatment of people who are bitten is unpleasant and expensive. Vaccination of animals rather than of humans is the best approach to control the disease. However, pre-exposure vaccination of certain parts of the human population, e.g. children, people in remote areas with no access to PEP may be needed to prevent rabies cases.

GAP: There is a need to develop and encourage health professionals to work together in a more coordinated fashion. Clearly, it is not possible to only vaccinate dogs as a means to save human lives. Much of the focus has therefore been on using PEP in humans. In many countries, agricultural services and human health services do not communicate. Development of more a more integrated sustainable strategy between relevant ministries is required.

Direct impact (a) on production

At present, the disease still causes remarkable economic damage through loss of animals destined for production, mainly in Latin America. In Brazil, bovine and equine herds are severely affected by the disease. In Africa, rabies in Kudus in Namibia causes severe financial losses to the agricultural sector.

GAP: The economic impact of rabies in cattle in Latin America has not been fully elucidated.

Direct impact (b) cost of private and public control measures

Can be high but depends on the situation in a specific country.

According to the US Centers for Disease Control, the estimated costs associated have risen to more than $300 million annually. These costs include the vaccination of companion animals, animal control programs, maintenance of rabies laboratories, and medical costs, such as those incurred for rabies post-exposure prophylaxis.

GAP: There is an urgent need to evaluate the economic burden of rabies globally and to evaluate the cost-effectiveness of intervention strategies.

Indirect impact

Limited

Trade implications

Impact on international trade/exports from the EU due to existing regulations
Assurances on rabies status are required for trade in live animals and products.

**Impact on EU intra-community trade due to existing EU regulations**

Assurances on rabies status are required for trade in live animals and products.

GAP: Illegal importation of dogs poses a threat to reintroduction of rabies into a previously rabies free zone.

**Impact on national trade due to existing regulations**

Limited

**Main perceived obstacles for effective prevention and control**

While there is the knowledge and tools to eliminate the threat of canine rabies the disease remains a public health threat in many parts of the world. Lack of motivation by governments, cultural issues and inadequate funding remain barriers. This is despite the number of human rabies deaths worldwide is greater than that from polio, meningococcal meningitis, Japanese encephalitis, yellow fever, SARS, bird flu and other scourges that attract more attention. For sylvatic rabies, multi-species reservoirs represent a challenge to disease control using oral rabies vaccines. Also, the vast areas in Eurasia and the Americas affected by wildlife-mediated rabies make it financially challenging.

GAP: Lack of educational awareness on all levels of society as to the rabies prevention. Agriculture and human health often do not work together or share information. Lack of financial support from international funding agencies. Dogs are not normally considered ‘food animals’ and are not valued highly, even though they do serve a valuable role in societies. No cost-effective vaccination strategies for elimination of wildlife-mediated rabies for vast territories are available yet.

**Main perceived facilitators for effective prevention and control**

Safe and effective vaccines are now widely available. It is the need to control rabies in dogs that must occupy most attention. The tools are available, but attitudes must change before they can be applied.

GAP: The over-population of dogs makes it seem impossible to implement rabies control programs in many resource poor countries. The role of animal welfare in removing dogs, even humanely, is often contentious. There is a need to develop safe and effective dog contraceptives to humanely reduce the existing dog population. Education is critical to improve support. Understanding the cost-effectiveness of rabies prevention is critical to convince governments to support national strategies.

**Risk**

Failure to control rabies in dogs in developing countries will result in continued high mortality each year and will create possibilities for spill-overs into wildlife. Targeted surveillance (indicator animals) should be established in all countries. Other reservoir hosts including chiroptera should be included as there a potential of spill-over into new hosts and/or reservoirs. In general, better surveillance and diagnostic facilities are required.

GAP: Need for cost-benefit analyses of the implementation of rabies prevention programs.

**Main critical gaps**

**Conclusion**
Cheap and safe vaccines for animals as well as humans have been developed. Oral vaccination of wildlife has been successful in Europe and is beginning to reduce the incidence of rabies among foxes and raccoons in the US. Oral vaccination of stray dogs could lead to the eradication of rabies in countries where dog rabies is the sole source of human exposure.

**Sources of information**

**Name of expert group leader**

Expert group members are included where permission has been given

Carolin Schumacher, Merial, France (leader)

Thomas Muller, Friedrich-Loeffler-Institut, Germany.

Debora Briggs, Global Alliance for Rabies Control, USA

Conrad Freuling, Friedrich-Loeffler-Institut, Germany.

Ariane Cagienard, Merial, France

**Name of reviewers**

Programme Management Board

**Date of submission by expert group**

**References**