Oral vaccination of dogs and wild carnivores

J. Barrat
- Requirements concerning the vaccinal virus
  - Safety
  - Efficacy
  - Local approval

- Requirements concerning the casing
  - Biomarker
  - Attractivity
Strains of virus used in oral vaccines

SAD P5/88 → AGA → SAD Bern → Passages on various cell cultures → ERA virus → Probability of reversion : $1:10^{-16}$ → VRG

SAD B19 → AAA → SAG1

SAD Bern passaged on BHK21 cells → GAA → SAG2

SAD strain isolated from a naturally infected dog in the USA in 1935

AGA, AAA, GAA : codons of the rabies strains
SAD : Street Alabama Dufferin
ERA : Evelyn (Gaynor), Rokitnicki, Abelseth
SAG : Street Alabama Gif : name of the laboratory (Gif) that performed the double mutation of the SAD strain
VRG : Vaccinia Glycoprotein Recombinant
Commercially available oral vaccines

- SAD Bern strain baits,
- SAD B19, SAD P5/88 baits,
- SAG baits (n° EU/2/00/021/001 and 002),
- VRG baits

Rectangular Fishmeal polymer VRG bait (France) for red foxes and raccoon dogs

Square Fishmeal or Chickenmeal Polymer VRG bait (USA) for raccoons, coyotes and gray foxes
Requirements for rabies oral vaccines


Rabies Vaccine (Live, oral) for foxes, Vaccinum rabiei perorale vivum ad vulpem, European Pharmacopoeia 2005, p 792.

WHO safety criteria for rabies vaccines

- IVth WHO/OIE Concertation meeting on rabies control in Europe, Piestany, 5-7 October 1993.
WHO quality criteria

- **Safety in the target and non target species:** namely wild rodents and other wild and domestic species and also in non-human primates.
  - Oral administration of ten times the recommended dose to at least 10 young (3 – 6 months old) animals of the target species, or in dogs less than 10 weeks of age.
  - Relevant local wild or domestic animal species that may consume baits should also be administered the field dose of vaccine orally in a volume adapted to body weight.

- **Safety in wild rodents:** at least 10 and if possible 50 of each of the most common local rodent species should be given the field dose of vaccine orally and intramuscularly. If the animals that are vaccinated become sick or die from rabies, the use of the vaccine should be re-evaluated.

- **Any rabies virus isolated from animals in vaccination areas should be characterized** using monoclonal antibodies or molecular techniques to ensure that no vaccine-induced rabies has occurred.
Quality criteria: European Pharmacopoeia

- **Safety in the target species:**
  - Oral administration of the field dose to 40 foxes: no sign of rabies for 180 days.
  - Oral administration of ten times the recommended dose to 10 foxes: no sign of rabies for 180 days.

- **Safety in non target species:**
  - Oral administration of ten times the recommended dose to 10 dogs: no sign of rabies for 180 days.
  - Oral administration of ten times the recommended dose to 10 cats: no sign of rabies for 180 days.

- **Safety in wild rodents:** in natural and experimental conditions.

- **Potency or efficacy:** Rabies challenge in 25 foxes vaccinated 6 months earlier including 10 control foxes: no sign of rabies in at least 23 vaccinees and at least 9 controls show signs of rabies.
Quality criteria: European Commission

- **Safety in target and non target species:** Same as those of European Pharmacopoeia and WHO.

- **Stability:**
  - **Bait casing:** The melting point of the bait casing should be above 40°C to ensure that the capsule of the vaccine is still covered.
  - **Vaccine titre:** The titre of the vaccine in the bait should not fall below the 100% protective dose following exposure to 25°C for seven days.
  - The use of the **most stable vaccine** should be preferred in situations where high stability is considered important.
  - **Each vaccine batch** should be tested and approved for titre and stability by an acknowledged quality control scheme according to OIE standards and WHO recommendations.
Innocuity criteria

Numerous species have been tested with the various candidate vaccines:

- **target species:**
  fox, dog, jackal, skunk, coyotes, racoon, racoon dog.

- **non-target species:** insectivora, non-human primates, herbivora (wild and domestic), wild boar, rodents, birds (several species including scavenger and birds of prey)
Residual pathogenicity of SAD strain: previous data

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>Paper reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse and other rodents</td>
<td>IC, IM, OR</td>
<td>Steck et al., 1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Winkler et al., 1976</td>
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<td></td>
<td></td>
<td>Wachendörfer et al., 1978</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leblois et al., 1988</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Artois et al., 1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vos et al., 1999</td>
</tr>
<tr>
<td>1 fox cub, 1 cat, 1 stone marten</td>
<td>OR</td>
<td>Wandeler, 1988</td>
</tr>
<tr>
<td>Skunks (7/11)</td>
<td>OR</td>
<td>Rupprecht, 1990</td>
</tr>
<tr>
<td>Baboons (2/4)</td>
<td>OR</td>
<td>Bingham et al., 1992</td>
</tr>
</tbody>
</table>
Residual pathogenicity of SAD strain: recent data

- One case of rabies induced by vaccinal SAD strain in Austria in 2004 (Rabies Bulletin Europe, 2004) and one case in 2006 (CPCASA, 2006).

- Four cases in Germany since several years (Ottawa, RITA meeting, 2005; FVO inspection, 2004).

- Sixteen cases in Canada from 1989 to 2004, including 4 red foxes, 2 raccoons, 2 striped skunks and one bovine calf (Brasilia, RITA meeting, 2006).
Safety of SAG and VRG vaccines

VRG:
- one clinical adverse reaction documented in a woman (Rupprecht et al., 1999): spontaneously cleared skin lesions as a result of exposure to the vaccine, through a bite while attempting to remove a partially chewed vaccine bait from a dog’s mouth.

SAG strains:
- SAG1 strain is experimentally pathogenic for suckling mice by intra-cranial route (Schumacher et al., 1993).

“Vaccine selection: vaccine efficacy in the target species needs to be considered. Preference should be given to vaccines with reduced (non-rabies related) pathogenicity, such as recombinant vaccines (VRG) or a highly attenuated live virus strain (SAG2), over more pathogenic attenuated live viruses for oral immunization of wildlife and dogs.” (WHO, 2005).
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>puppies</th>
<th>Other carnivora</th>
<th>Non human primates</th>
<th>rodents</th>
<th>Immuno-compromised mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRG</td>
<td>21 puppies $10^{10}$ TCID$_{50}$</td>
<td>no path. Numerous species</td>
<td>10 chimpanzees $10^9$ TCID$_{50}$</td>
<td>no mortality</td>
<td>no mortality 40 SCID mice $10^9$ TCID$_{50}$</td>
</tr>
<tr>
<td>SAG2</td>
<td>10 puppies $10^9$ TCID$_{50}$</td>
<td>no path. Numerous species</td>
<td>10 baboons $10^9$ PFU</td>
<td>no mortality</td>
<td>no mortality 10 SCID mice $10^8$ TCID$_{50}$</td>
</tr>
<tr>
<td>SAD B19</td>
<td>12 Puppies $10^{8.6}$ FFU</td>
<td>Pathogenic for skunks</td>
<td>10 chimpanzees 12 baboons $10^{8.3}$ FFU</td>
<td>up to 6% mortality several species</td>
<td>mortality : 2/10 nude mice $10^{7.3}$ FFU</td>
</tr>
<tr>
<td>SAD Bern</td>
<td>Path. for fox cubs</td>
<td>Path. for cat, fox, stone marten</td>
<td>2/4 baboons die with one bait</td>
<td>mortality</td>
<td></td>
</tr>
</tbody>
</table>
Stability of bait casing and of vaccine titre

All rabies strains are equally sensitive to temperature but appropriate preservatives and casings may create a difference between vaccines.

Collaborative European field trial (Mutinelli et al., unpublished data June 2000)
Rabies oral vaccination of foxes: key dates

- **1971-1976**: Experiment in USA and Canada demonstrate that attenuated rabies SAD strain immunises foxes when orally administered in baits (Baer and al., 1971; Baer 1975; Black and Lawson, 1973; Debies and al., 1972; Winkler and Baer, 1976).

- **1977**: First field trial in Europe (Switzerland) with SAD-Bern virus in chicken-head baits in an Alpine valley: demonstration of the feasibility, safety and efficacy of the method (Steck et al., 1980).

- **1983**: First field trials using SAD-B19 strain in chicken-head baits in Germany, then in 1985 the same strain is included in machine-manufactured baits (Schneider et al., 1983).

- **1985**: First field use in southern Ontario (Canada) of SAD-Bern.

- **1986**: First vaccination campaigns using SAD-B19 strain in France and Luxembourg (Artois et al., 1987); first vaccination campaign using VRG in France (Blancou et al., 1986).
Experimental field studies conducted with photographic traps and track identification (M. Artois and S. Ruette) have shown that less than 10% of baits are consumed by the fox 'target species'. It means that 90% of baits are eaten by "non-target" species.

⇒ great importance of safety studies in target and non-target species
Importance of fox cub vaccination

Index of fox population density

TC+

TC-

⇒ studies in farmed animals (FAIR project)
⇒ test of different baiting strategies in the field
General organisation of the campaigns

- Compartmentalization of the contaminated area using natural and artificial barriers
  - to repeat vaccination until rabies elimination is confirmed and for protecting rabies-freed areas
  - to establish concerted plans of vaccination with neighboring countries: fly over the border and drop baits on both sides!

- Rabies ignores national borders!
General organisation of the campaigns

- WHO expert committee on Rabies, Eight Report, 1992, (page 45) :

"International cooperation in border areas is essential at all levels to achieve effective vaccination programs. Neighbouring countries should carefully coordinate their activities along common borders. If field trials reach a country border, local administrative staff from both countries should coordinate their efforts. "
Choice of period of distribution

- Double bait distribution with both SAG 2 and VRG baits in caged foxes (FAIR project, Lambot et al., Vaccine, under press): the humoral responses to oral vaccination with either SAG 2 or VRG vaccines are not significantly increased when repeating vaccination 35 days later.

- Two unique vaccinations (with only one distribution per campaign) in late Spring and in Autumn.

Global yearly bait density = 40 baits/ km² when aerial distribution.
Strategy of vaccine-bait distribution

- Uniform distribution of 20 baits / km²
- Aerial distribution
  - Lines every 300-500m
  - Altitude=100-150 m (GPS)
  - 100-150 km/h
- Manual
  - Lines every 300-500m
- Twice a year (spring - autumn)
- Cross border cooperation
WHO expert committee on Rabies, Eight Report, 1992:

"Most field trials with oral vaccination employ three methods of evaluation: testing for the occurrence of a biomarker (usually tetracycline), which is incorporated into the bait, in the target species; examining sera from the target species for rabies virus-neutralising antibody; and analysing the incidence of rabies in animals before and after the programme.

... Whenever feasible, only freshly collected sera should be used for virus-neutralising antibody titration..."
Monitoring titre in baits

- A control titration is essential as soon as the tender is done and before delivery in the storage area.
- Titrations should then be performed before the beginning of the campaign and at random when the helicopter or the plane lands after a baiting session.
Conclusion

In Europe, fox mediated rabies can be eradicated / eliminated by using an appropriate strategy of oral vaccination supported by validated and continuously monitored field and laboratory techniques.
Thanks to oral vaccinations of foxes, rabies has been eliminated from large areas.
1- When organized in all contaminated areas, oral vaccination of foxes has allowed to eliminate rabies within 3 to 5 years

2- The cost/efficiency analysis of experimental and field protocols helps to choose a well adapted strategy, especially in emergency situation
Cost-benefit of oral vaccination

A cost-effectiveness study of rabies eradication in Switzerland (Zanoni et al., 2000) and in France (Aubert, 1999) has been done:

- In Switzerland, only 3.1% of the direct costs of rabies were for the vaccine baits (SAG2) in 1993.

- In France, the balance was positive for oral vaccination after the fourth year of the programme, and the costs of baits (SAG2 and VRG) were negligible compared to the costs of preventive vaccination of pets and prevention in humans.
Benefits of elimination of fox-related rabies in Europe

- Improvement in public health
  - Decrease of the number of human post-exposure prophylaxis

- Improvement in animal health
  - Reduction of domestic animal mortalities and associated economical losses (cattle)
  - Repopulation of locally threatened wild species (badger)
  - New regulations regarding imports of pet dogs and cats from certain infected countries to rabies-free countries
  - Quarantine measure replaced with rabies vaccination followed by serological testing (pet travel scheme)
Possible causes of setbacks

- Too small vaccination zone around residual foci
- Oral vaccination stopped too early after the last recorded case or not applied on a regular basis (twice a year)
- Delayed or lack of coordination between neighbouring countries / provinces
- Inappropriate strategy in the field
- Lack of control in the field
- Inappropriate monitoring of the vaccination efficacy
  - Incidence of rabies
  - Bait uptake
  - Seroconversion
Success of oral vaccination programmes

Before starting OVF…

- Long term financial means
- Knowledge of the target population

Technical means

- Type of vaccines and baits
- Method of release

General strategy

- Distribution patterns
- Seasonal pattern
  - Bait density
- Control of baits during campaign

Efficacy follow up

- Adequate surveillance
- Standardised laboratory tests (diagnosis and serology)
- Fox density monitoring (hunting bags, night counting index)
Oral vaccination of dogs

- The preferential vaccination mode should be parenteral
- Oral vaccines is intended to be used when there is a high proportion of inaccessible dogs

- Prerequisites
  - Field studies are needed to evaluate the stray and poorly supervised proportions of the dog population
  - Field studies are needed to define the adequate distribution technique
In India
Importance of knowledge of population

- Distribution trial in rural India
  - When a dog is asleep, it is generally not hungry and then does not pay attention to the bait.
  - The baiting period should ideally take place when all dogs are active and not yet fed by people.
  - In order to avoid any competition between dogs, when baiting a pack of several dogs
    - all dogs should be given a bait at the same time.
    - if another dog joins the group after baiting, it should be baited afterwards and separately if possible because it is usually frightened to be bitten by the others or a dog that ate recently a bait may try to eat other baits.
  - Monkeys have been observed both in the rural and in the urban areas. It is then essential to fulfil the WHO recommendations concerning safety for oral vaccination of dogs against rabies, “Only vaccines with the lowest known residual pathogenicity (SAG2 and VRG) should be used in dogs.”
- With these precautions bait acceptance passed from 60-63 to 79% (N=100)
In Morocco
Amman, Jordan, 23-25 June 2008

Thank you for your attention