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Korrespondenzadresse:
thomas.mueller@fli.bund.de

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Institute of Epidemiology, Friedrich-Loeffler-Institut, Wusterhausen, Germany[1]
Federal Ministry of Food, Agriculture and Consumer Protection, Bonn, Germany[2]
IDT-Biologika GmbH, Dessau-Rosslau, Germany[3]
Institute of Molecular Biology, Friedrich-Loeffler-Institut, Greifswald – Insel Riems, ermany[4]

Elimination of terrestrial rabies in Germany using oral vaccination of foxes

Tilgung der Fuchstollwut in Deutschland mithilfe der oralen Immunisierung

Thomas Müller[1], Hans-Joachim Bätza[2], Conrad Freuling[1], Anke Kliemt[1], Jeannette Kliemt[1], Rolf Heuser[2], Hartmut Schlüter[1], Thomas Selhorst[1], Adriaan Vos[3], Thomas C. Mettenleiter[4]

Summary

Oral rabies vaccination (ORV) has become the method of choice in fox rabies control in Europe. During the past three decades fox-mediated rabies virtually disappeared from Western and Central Europe. Following Switzerland, Germany was the second European country to launch ORV field trials on its territory in 1983. This paper provides a historical overview on the emergence of fox rabies in Germany; describing the basic principles and milestones of the German rabies eradication programme and presenting results of two decades of efforts to control the disease in foxes. Also, setbacks as well as country-specific differences and particularities on Germany's long way to rabies elimination in comparison to other European countries are addressed. Since the first field trials in Germany the number of rabies cases steadily decreased from 10 484 in 1983 to three cases recorded in 2006. On February 3rd 2006 the last case of terrestrial rabies in Germany was detected in a fox near the town of Mainz, Rhineland-Palatinate. In 2008, ORV ceased after 25 years and Germany was officially declared as free from terrestrial rabies. The German rabies eradication programme did cost approximately 100 million euro of which 37 million euro were covered by the EU. For the future, efforts should focus on maintaining a rabies free status by implementing measures to prevent reintroduction of terrestrial rabies from endemic countries.

Keywords: fox rabies, elimination, Germany, oral rabies vaccination, vaccination strategy, costs

Zusammenfassung

Die orale Immunisierung der Füchse (OIF) ist die Methode der Wahl zur Bekämpfung der Fuchstollwut in Europa. Während der vergangenen drei Jahrzehnte konnte die Fuchstollwut in weiten Teilen West- und Mitteleuropas getilgt werden. Dieser Artikel gibt einen historischen Überblick über die Entwicklung der Fuchstollwut in Deutschland. Es werden die grundlegenden Prinzipien, Meilensteine, Ergebnisse aber auch Rückschläge des deutschen Bekämpfungsprogrammes beschrieben und auf länderspezifische Unterschiede und Besonderheiten auf Deutschlands langem Weg zur Tollwutfreiheit eingegangen. Seit dem ersten Feldversuch im Jahr 1983 sank die Zahl der Tollwutfälle kontinuierlich, von anfänglich 10 484 auf drei Fälle im Jahr 2006. Am 3. Februar 2006 wurde der letzte Fall von Tollwut in Deutschland bei einem Fuchs in der Nähe der Stadt Mainz, Rheinland-Pfalz diagnostiziert. Im Jahr 2008, 25 Jahre nach Beginn, wurde die OIF eingestellt und Deutschland offiziell als frei von terrestrischer Tollwut erklärt. Das deutsche Tollwutbekämpfungsprogramm verursachte Kosten von ca. 100 Millionen Euro, von denen ca. 37 Millionen Euro von der EU rückerstattet wurden. Zukünftig liegt der Schwerpunkt auf der Aufrechterhaltung des Tollwut-freien Status und beinhaltet vorrangig Maßnahmen zur Verhinderung der Wiedereinschleppung der Tollwut aus endemischen Ländern.

Schlüsselwörter: Fuchstollwut, Tollwut, Tilgung, Deutschland, orale Immunisierung, Impfstrategie, Kosten

Introduction

Rabies is a fatal zoonotic disease caused by negative single stranded RNA viruses of the genus *Lyssavirus*, family *Rhabdoviridae*, order *Mononegavirales*. It is generally transmitted by bite from an infected mammal. Recognized etiological agents consist of several different virus species, of which the vast majority have *Chiroptera* as reservoir hosts (Dietzgen et al., 2011; Freuling et al., 2011; Kuzmin et al., 2010). Rabies caused by the prototypic classical rabies virus (RABV) is found across the world, with the exception of Antarctica and Australia, and has its reservoirs in several species of the order *Carnivora*, and also in bats in the Americas (World Health Organisation, 2005). Two epidemiological forms, i. e. dog-mediated and wildlife-mediated rabies also referred to as urban and sylvatic rabies, respectively, can be distinguished. Dog-mediated rabies causes the highest burden for both human and animal health worldwide. It is responsible for millions of suspect human exposures with an estimated 55 000 human rabies deaths annually, in particular in Africa and Asia. Wildlife-mediated rabies with a variety of wild carnivore reservoir species is a predominant problem in the northern hemisphere (World Health Organisation, 2005). In Europe, sylvatic rabies is supposed to have emerged from a focus South of Kaliningrad during World War II, where the disease quickly established itself in the fox population. Subsequently, the red fox (*Vulpes vulpes*) became the main reservoir inexorably spreading the disease across the continent within a few decades (Taylor, 1976). Early attempts to control fox rabies using conventional methods aimed at a drastic decimation of the fox population below a certain threshold in order to interrupt the infectious cycle failed (Aubert, 1992). It was not until the mid 1980s that oral rabies vaccination (ORV) of foxes using modified live rabies virus vaccines had been developed into the method of choice in rabies control in Europe. Within 28 years after first field trials in Switzerland (1978) this method of disease control in wildlife resulted in virtual elimination of fox rabies in Western and Central Europe and in a substantial decrease in rabies incidence in Eastern European countries (Müller, 2000; Rupprecht et al., 2008). To date, ten European countries have been officially recognised as being free of terrestrial rabies due to ORV, i. e. Finland (achieved rabies free status in 1991), the Netherlands (1991), Italy (1997 but lost status in 2008), Switzerland (1998) (Breitenmoser, 2000; Zanoni et al., 2000), France (2000, regained the status again in 2010 after losing it in 2008), Belgium and Luxembourg (2001), the Czech Republic (2004) (Cliquet and Aubert, 2004; Matouch and Vitasek, 2005). In 2008, Germany and Austria joined the list and were declared free of terrestrial rabies according to OIE standards (Office International des Epizooties, 2008).

This paper provides a historical review on the emergence of fox rabies and the national approach to control fox rabies in Germany with special emphasis on ORV starting with the first field trials in 1983 and ending with the successful elimination of fox rabies in 2008, thereby re-assessing Germany's long way to rabies elimination.

Historical background

In Germany, rabies had been present for centuries posing a serious threat to human health. It is suggested that in the early history of Germany rabies could not be classified simply as urban or sylvatic as it was a mixture of the two types depending on the conditions present at any given time. There are reports, for instance, of large outbreaks of rabies in wolves and widespread fox epizootics in the southern parts of Germany dating from 1271 and the early 1800s, respectively (Müller et al., 2004). However, with increasing urbanisation dog-mediated rabies became more and more a problem. Already in the late 1700s the Prussian King Frederic I and the Duke of Wuerttemberg issued decrees describing preventive measures for controlling urban rabies such as muzzling and yearly inspection of dogs, nightly curfew and destruction of old or sick animals as well as of stray dogs (Müller et al., 2004). Notification of rabies and strict implementation of hygienic measures as laid down in the Ordinance concerning the Defence and Rejection of Livestock Diseases as of June 23, 1880, resulted in a virtual disappearance of dog-mediated rabies in Germany (except for areas bordering certain neighbouring countries at the time) at the beginning of the 20th century (Anonym, 1880; Müller et al., 2004). In 1939, the territory comprising Germany as it exists today was considered free of dog-mediated rabies. However, soon after World War II fox rabies emerged again and became an increasing problem (Taylor, 1976).

Already in 1947, the fox-mediated rabies front arrived in the north-eastern corner of Germany after it had crossed the Odra River and rapidly moved westwards into northern Germany. In 1951, a second rabies wave reached Germany in South-Eastern Bavaria, where rabies emerged in foxes in the border area with Austria and the former Czechoslovakia. In subsequent years, rabies spread all over the country and the disease dramatically progressed as in many other parts of Europe as well (Wachendörfer and Frost, 1992). As a result, the number of reported rabies cases steadily increased nationwide from 1947 until the beginning of the 1980s, when fox rabies reached its western and south-easternmost expansion in Europe. Between 1947 and 1981, a total of 17 human rabies cases were reported in Germany of which nine could be attributed to fox-mediated rabies acquired in the country. Due to its strong impact on public health considerable efforts were made to increase surveillance and provide a legal basis for nation-wide rabies control. In West Germany, the national Ordinance on the Protection against Rabies (Rabies Ordinance) dated 11 March 1977 (Federal Law Gazette I, 444) laid down vaccination to be conducted using inactivated rabies vaccines and, for the first time, preventive measures to control rabies in wildlife (Anonym, 1977). In the former German Democratic Republic (GDR) preventive measures against rabies in domestic and wild animals were laid down in two separate instructions (Anonym, 1974a; Anonym, 1974b). At the time, conventional methods of wildlife rabies control aimed at a drastic decimation of the fox population to reduce its density below a contact threshold (R0) where disease transmission would be interrupted (R0 < 1) (Aubert, 1992; Manz, 1979). Besides intensive culling additional measures to reduce the fox population could be ordered by competent authorities. These included attempts of hormonal sterilization, poisoning, trapping, digging, gassing of fox dens, and destroying of fox cubs at dens (Anonym, 1977). None of these methods, however, was successful in reducing and maintaining the fox population below this endemic threshold (Aubert, 1992). In contrast, they were suggested as counterproductive as a result of disruption

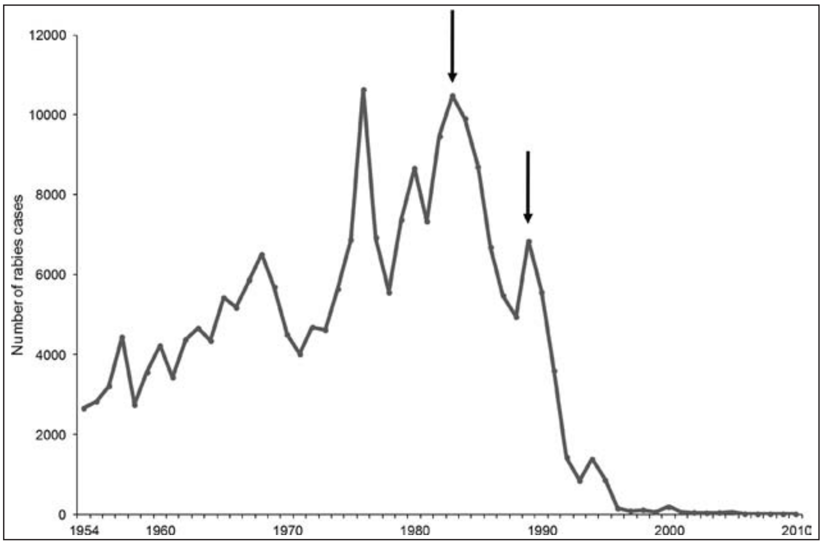

FIGURE 1: *Development of rabies incidence in Germany (1954–2010) and implementation of ORV campaigns in Germany (indicated by arrows).*

of the social system thereby increasing contacts between animals and, hence, the rabies incidence. With 10 634 and 10 484 reported cases in wildlife and domestic animals, the rabies incidence reached peaks in 1977 and 1983, respectively. Thus, Germany had the highest rabies incidence reported in Europe at that time, which might also partly be attributed to efficient surveillance (Fig. 1).

The German national ORV eradication program – basic principles

Legal basis and implementation of oral vaccination of foxes

The change from urban to sylvatic rabies made animal disease control far more complex and represented a great challenge to all stakeholders involved (Wandeler et al., 1988). Considering the failure of conventional methods to control fox rabies and the fact that mass culling of wildlife was no longer acceptable, a paradigm shift was urgently required. When in the 1970s it was experimentally shown that red foxes could be orally immunized against rabies using attenuated rabies viruses (Baer et al., 1971; Black and Lawson, 1973; Debbie et al., 1972), the concept of orally vaccinating wildlife against rabies using modified live virus vaccines offered a new perspective for fox rabies control (Wandeler et al., 1988). Yet many practical issues had to be solved for successful implementation of ORV under field conditions such as the development of (i) efficacious and safe oral rabies virus vaccines, (ii) suitable vaccine blisters, (iii) attractive baits, (iii) adequate bait markers, (iv) efficient baiting strategies and (v) the identification of epidemiological and ecological parameters pertinent to rabies elimination (MacInnes et al., 1988). In Europe, the first ORV field trial was successfully conducted in Switzerland in 1978 demonstrating the practicability of this method under field conditions (Steck et al., 1982). Already five years later, West Germany as the second European country launched similar field trials in the federal states of Hesse and Bavaria in spring 1983, followed by Baden-Wuerttemberg in autumn 1983, and Lower Saxony and Schleswig-Holstein in spring 1984 (Frost et al., 1985; Schneider and Cox, 1983). Encouraged by the success obtained by the end of 1987, ORV was implemented in all western federal states except the city states with field trial areas steadily increasing in size. In the GDR, the first ORV field trials were conducted on the Isle of Rügen and the former district of Gadebusch in the northwest of what is now Mecklenburg-Western Pomerania in autumn 1989 (Stöhr et al., 1990b). One year later new field trial areas were established in the federal states of Thuringia and Brandenburg. Whereas in Western Germany field trials were performed until the end of the 1980s, due to increasing political pressure field trials in East Germany were immediately turned into a national rabies control program (Fig. 2). Commission Decision 89/455/EC on co-financing of costs for disease eradication issued in 1989 was a milestone for fox rabies control in Europe as the European Union (EU) offered a financial incentive for implementation of ORV pilot programmes in Member States (MS). For EU approved programmes 50% of the costs for purchase of vaccine baits and bait distribution were subject to reimbursement. Furthermore, funding of up to 10 000 euro was granted for small-scale pilot projects in regions where non-governmental organizations distributed baits free of charge (Anonym, 1989). Two years later, ORV became an integral part of the national Ordinance on the Protection Against Rabies dated 23 March 1991 (Federal Law Gazette I, 1168) as an additional rabies control measure in Germany, whilst gassing of fox dens was abandoned. This legislation determined the size of vaccination areas, the use of standard diagnostic procedures, sample sizes for rabies surveillance, monitoring of ORV in affected areas, and protection of vaccinated dogs. For the first time, the Federal Research Centre for Virus Diseases of Animals (BFAV – present day: Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health [FLI]) was given a leading role in ORV campaigns in legal terms because competent authorities had to consult with the BFAV when determining the timing and location of oral immunisation. The ordinance was amended in 2000 by further

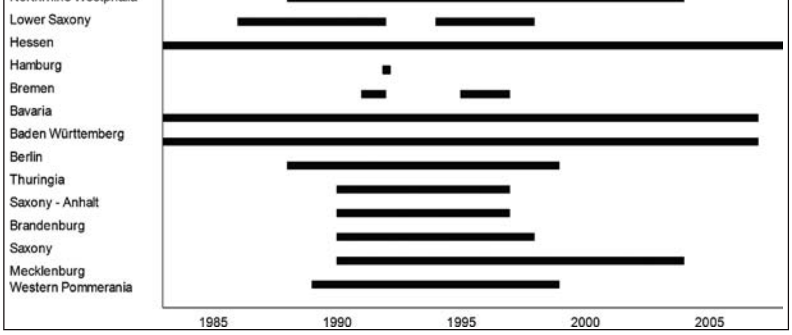

FIGURE 2: *Start and cessation of ORV campaigns in German federal states (1983–2008).*

substantiating those measures enabling competent authority to declare an area of a size of at least 5000 sqkm as free from rabies if, subject to certain epidemiological scenarios, rabies had not been officially recorded there over a period of two and four years, respectively. This amendment newly stipulated that, besides epidemiological aspects and specific structural elements of landscapes, the competent authority also had to coordinate with the FLI the type of vaccine bait delivery, the vaccination strategy, the number of vaccine baits per sqkm and cessation of ORV campaigns. Both Rabies Ordinances dated 1991 and 2000 were re-formulated in April 2001 to improve readability (Rabies Ordinance in the version promulgated on 11 April 2001 (Federal Law Gazette I, 598). The Rabies Ordinance was further amended again in 2004 and 2005. The last federal states to implement ORV were the city states of Hamburg and Bremen in 1992 and 1993, respectively (Fig. 2).

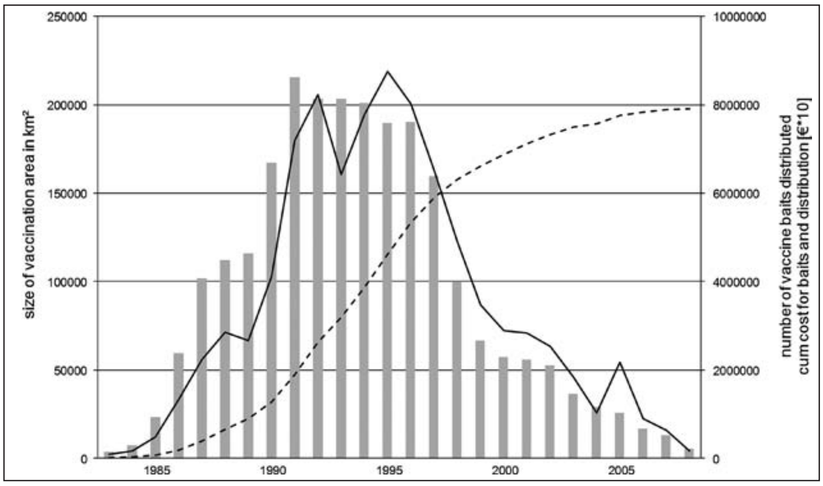

FIGURE 3: *Development of the size of vaccination areas (bar chart), number of baits used per year and cumulative direct costs (vaccine baits and bait distribution – dashed line) from the beginning of ORV in 1983 until cessation of campaigns in 2008.*

Vaccine baits

In Germany, three different SAD (Street Alabama Dufferin) Berne-derived attenuated rabies virus vaccines strains were developed, registered and used in ORV campaigns, i. e. SAD B19, SAD P5/88, and SAD VA1. Although SAG2 was also licensed in Germany through an EMA registration it was never used. The efficacy and safety of SAD B19 and SAD P5/88 based vaccines had been intensively studied (Kintscher et al., 1990; Neubert et al., 2001; Schneider and Cox, 1983; Sinnecker et al., 1990; Vos et al., 2000b; Vos et al., 1999). During 1983 and 2008 about 90 200 000 vaccine baits were distributed nationwide. SAD B19 was the most widely used vaccine virus strain followed by SAD P/88 and SAD VA1 with a total of 52 213 281; 37 444 481 and 542 014 vaccine baits distributed in the field, respectively (Tab. 1, Fig. 3). SAD VA1 was exclusively used in North Rhine-Westphalia between 1997 and 2002, before the license expired. Initially, from 1983 to 1985 free living foxes were immunized using chicken heads as baits. The increasing size of the vaccination areas, however, demanded high numbers of baits and, hence prompted intensive research into alternative baits. This led to the development of a machine-made bait known as the "Tübingen bait" in 1985: The vaccine blister or capsule containing SAD B19 was embedded in a bait casing based on animal fat, paraffin and meat and bone meal. When after the BSE-crisis products from terrestrial animals were no longer permitted they were replaced among others by fish meal (Müller et al., 1993b; Schneider et al., 1987; Stöhr et al., 1990c; Vos et al., 2004). While the first SAD P5/88 vaccine blisters were initially coated differently, subsequently the same bait casings were used as for SAD B19. Also, biscuits had been developed in which the vaccine sachet was placed inside (SAD VA1).

Bait density

Generally, the calculation of the bait density needed to achieve sufficient vaccination coverage in foxes was rather an empirical than a scientific approach. Initially, it was assumed that 10–15 baits were needed per animal targeted (Linhart and Kenelly, 1967). Thus, in the first years of the ORV field trials (early 1980s) 12–15 baits/km² and campaign were regarded sufficient (Schneider et al., 1987). Increasing fox and wild boar populations soon required an adaptation of the bait density. Yearly hunting

TABLE 1: *Number of vaccine baits distributed per federal state in five year intervals (1983–2008)*

Federal state	1983–1985	1986–1990	1991–1995	1996–2000	2001–2005	2006–2008	Total
BB		86 000	5 517 600	2 222 580			7 826 180
BE		18 847	64 000	44 472			127 319
BW	164 576	2 657 040	4 418 756	2 583 020	878 852	361 221	11 063 465
BY	270 016	3 710 176	4 082 207	2 457 244	1 248 597	377 364	12 145 604
HB			39 573	8623			48 196
HE	204 849	1 939 520	2 910 423	3 292 228	2 656 632	650 478	11 654 130
HH			9146				9146
MV		279 760	4 037 632	1 718 533			6 035 925
NI		1 527 411	1 304 090	261 952			3 093 453
NW		599 916	1 724 957	3 383 942	1 986 378		7 695 193
RP	52 000	1 108 902	3 261 735	3 926 717	1 468 869	308 687	10 126 910
SH	30 800	192 508	67 624				290 932
SL		186 800	268 262	828 688	258 154		1 541 904
SN		199 800	3 298 187	3 134 264	1 892 823		8 525 074
ST		269 000	3 643 260	829 885			4 742 145
TH		407 000	3 744 000	1 123 200			5 274 200
total	722 241	13 182 680	38 391 452	25 815 348	10 390 305	1 697 750	90 199 776

statistics of foxes as well as of potential bait competitors; in particular wild boar were used to estimate the overall density. Subsequently, an appropriate bait density per campaign was determined. During 1987 and 2004, the bait density was increased to 18–25 baits/km² per campaign. In the final phase of the ORV programme (2004–2008), due to severe setbacks especially in long-term vaccinated areas an average bait density of about 25–30 baits/km² per campaign was used (Müller et al., 2005). Depending on the number of vaccination campaigns conducted per year the minimum and maximum number of baits distributed in an ORV area per km² and year ranged between 15–30 baits, and 30–150 baits for the time periods 1983–2001 and 2002–2005, respectively.

Time point of bait distribution

In principle, baits were distributed twice a year at the end/mid of March/April and September/October, respectively taking fox ecology as well as vaccine related issues into account. For instance, early spring and autumn when fox density is lowest and dispersal of juveniles occurs were considered favourable for vaccination. Also, the temperature stability of vaccine baits had to be considered as extreme temperatures in summer (melting of bait casing) and winter (liquid vaccine frozen) prevented optimal herd immunity in foxes. In certain areas, however, increasing fox densities resulted in dissatisfactory results of ORV campaigns, stagnation and setbacks. It was assumed that the absolute number of foxes not having consumed a bait after spring campaigns had increased considerably, in particular in fox cubs (Pastoret et al., 2004). To increase the overall vaccination coverage and cope with none-immune fox cubs in six federal states (Baden-Wuerttemberg, Bavaria, Rhineland-Palatinate, Saarland, Saxony, Schleswig-Holstein) between 1989 and 2005 additional ORV campaigns were conducted in late spring/early summer (Schlüter and Müller, 1995). For example, in 1997 and 1999 in Lower Saxony and North Rhine-Westphalia baits were directly placed at the entrance of known fox dens at the beginning of May in addition to the usual vaccination campaign in spring. Although the bait-uptake in juvenile foxes could be increased by den baiting it was still speculative if this also resulted in a protective immune response. Experimental studies showed that maternally transferred immunity resulted in a partially impaired immune response to vaccination in fox cubs less than eight weeks old resulting in an insufficient protection against rabies (Müller et al., 2001), and den baiting was replaced by summer distribution of baits in June. However, even summer distribution could not substantially increase the vaccination coverage in juvenile foxes (Vos et al., 2001b).

Mode of bait distribution

Initially, baits were exclusively distributed by hand with the assistance of local hunters. This approach became

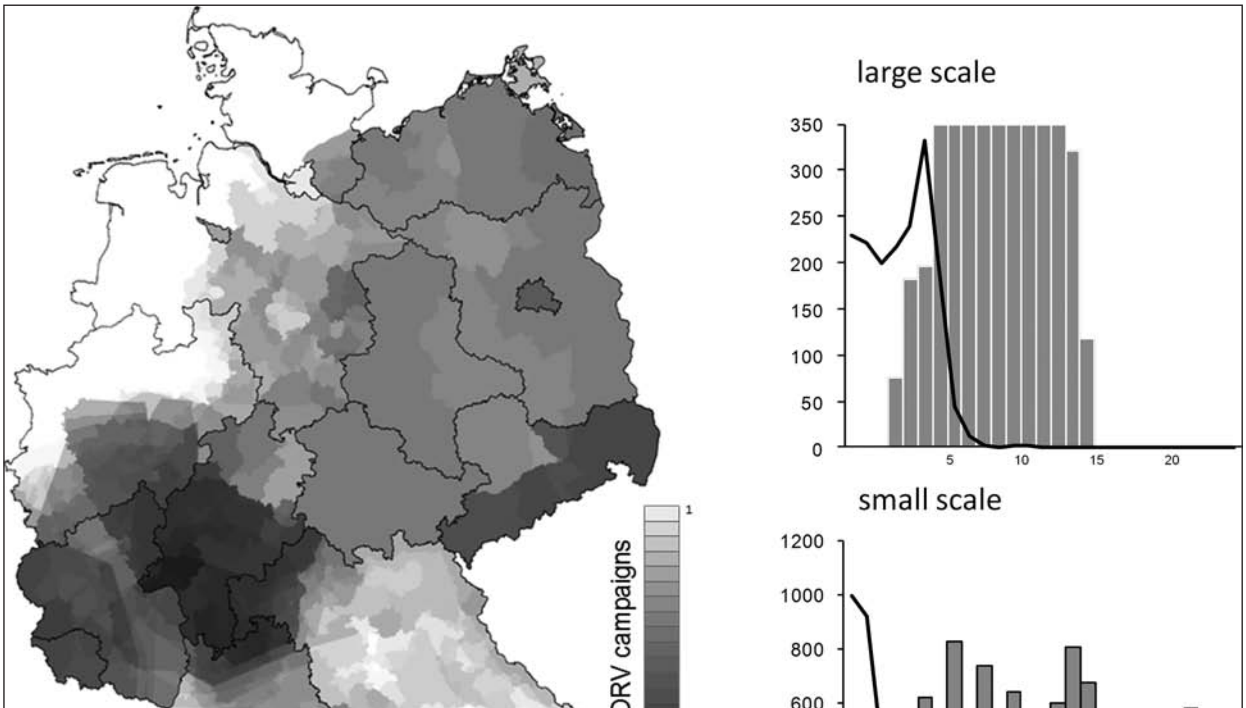

FIGURE 4: *Area ever covered with vaccine baits during 1983 and 2008. Darker colors reflect higher number of ORV campaigns needed until rabies elimination. Examples for small-scale and large-scale vaccination approaches in Germany and the effect on time and number of vaccination campaigns needed to eliminate rabies in a certain area (right).*

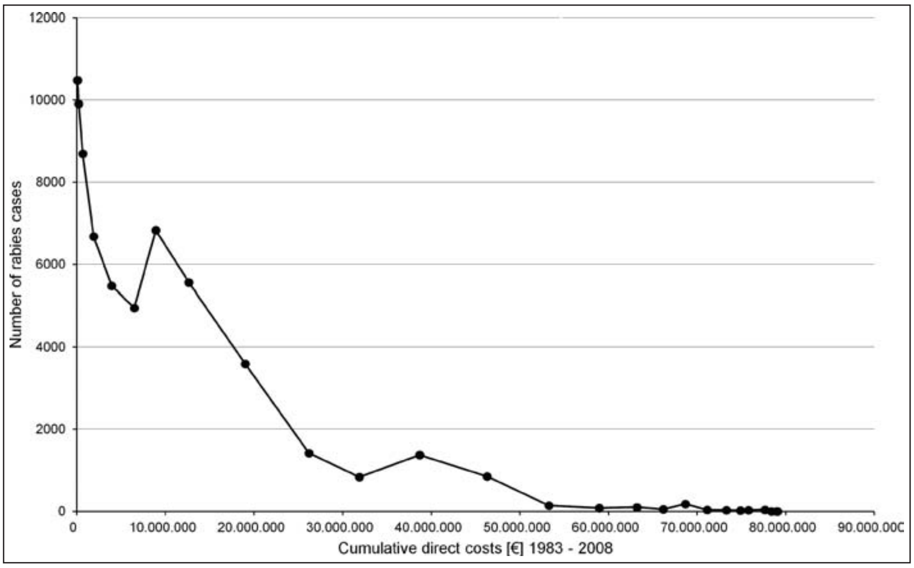

FIGURE 5: *Development of rabies cases as a result of direct cumulative costs spent for ORV campaigns in Germany between 1983 and 2008.*

known as the "Bavarian model", which set decisive standards at an international level (Schneider, 1984). Although hunters were relatively easily motivated, manual distribution of baits was laborious and time consuming requiring thorough preparation of suitable maps to (i) define the size of the areas to be covered with baits by individual hunters based on hunting areas, (ii) identify accessible fox habitats to be covered outside hunting areas, and (iii) mark the exact location of the baits (Schneider, 1989; Stöhr et al., 1990b). In Germany, large scale manual distribution of baits was mainly applied in federal states and city states (Berlin, Hamburg and Bremen) until 1991 and 1999, respectively. The drastic enlargement of vaccination areas in the 1990s together with an increasing numbers of baits to be distributed made manual campaign logistics increasingly complicated. The long-term demand for human resources could no longer be met, and a growing weariness of hunters to distribute baits after several campaigns was observed in certain areas, resulting in decreasing vaccination coverage of foxes (Schneider, 1990; Stöhr et al., 1994). A decisive breakthrough for large-scale ORV campaigns in Germany was the implementation of aerial distribution of baits as an alternative, sustainable and more cost-effective way in the mid of 1980. The use of fixed-wing aircraft was initially tested in a swamp-like area in the border region of the districts Weilheim Schongau, Bad Tölz and Garmisch-Patenkirchen in Bavaria in 1987. In the same year, a residual rabies focus in Aschaffenburg, Bavaria, was targeted aerially, and since 1991 this mode of bait distribution had become the method of choice at a national level (Müller et al., 1993c; Schneider, 1989). Baits were mainly distributed using fixed-wing aircrafts (Cesna, Piper, Z37). The use of helicopters was mostly restricted to densely populated areas, i. e. Ruhr area in North Rhine-Westphalia, at the end of 1990s and the beginning of the 2000s. In general, an average flight altitude of 150 meters above ground and a flight line distance of 1000 m was used (Müller et al., 1993c). Between 1995 and 2003 in seven federal states, i. e. Baden-Wuerttemberg (1995–1996, 2000–2003), Bavaria (1996, 1998–2003), Hesse (1997–2002), North Rhine-Westphalia (2001–2003), Rhineland-Palatinate (1996–2000), Saarland (1997–1999) and Saxony (1997–2003) baits were distributed twice during the spring and autumn campaigns at time intervals of 14 days using perpendicular flight lines to achieve better vaccination coverage in the fox population (Breitenmoser and Müller, 1997; Müller et al., 2005). To obtain a more homogenous spatial distribution of baits on the ground by considering home range sizes the strategy was changed nationwide in 2003 and flight line distance was reduced to 500 m.

In the early years of aerial distribution baits had to be manually dropped from aircrafts (Müller et al., 1993c). Since the early 2000s aerial distribution was optimized using computer-supported fully automated dropping systems (SURVIS) connected to GPS with the latter allowing precise GIS documentation of bait droppings (Vos et al., 2001a). Recording of exact coordinates of bait droppings using GIS for the first time allowed a quality assessment of the method in terms of deviations from intended flight-line distance, bait density on the ground and identification of non-flying zones (Gschwender et al., 1996). Aerial distribution proved to have crucial advantages over manual distribution of baits as it (i) needed less organisational expenses and man power and was therefore more cost-effective, (ii) enabled large-scale vaccination and accessibility to difficult terrain, (iii) allowed quality assessment of the bait distribution and most importantly (iv) resulted in higher vaccination coverage, e. g. bait-uptake and immunization rates, in the target population (Müller and Selhorst, 2007; Müller et al., 1993c; Stöhr et al., 1994). Nevertheless, hand distribution of baits remained an essential complementary measure in nearly every ORV campaign, especially in areas with a high density of settlements and non-flying zones.

Vaccination strategy (selection of vaccination areas)

In contrast to Switzerland, where vaccination areas were established by compartmentalization regarding natural barriers (Breitenmoser et al., 2000; Zanoni et al., 2000), in Germany, the spatial component of the vaccination strategy followed a more heterogeneous approach at a federal state level. This applied to the spatial setting of areas to be vaccinated in time, the size of vaccination areas, and the size of the overlapping area in consecutively vaccinated areas as well as to the number of consecutive ORV campaigns conducted. Based on those parameters two different vaccination strategies were used (Schlüter and Müller, 1995; Selhorst et al., 2005). Due to more fragmented landscape features and limited budgets the great majority of federal states mainly used small-scale vaccination (Fig. 4). A key feature of this strategy was that the size and spatial settings of vaccination areas were frequently adapted to the temporal presence/absence of rabies cases in a given area. This approach resulted in a patchy pattern of vaccination areas that permanently changed spatially in consecu-

TABLE 2: *Rabies Surveillance in Germany. Total number of animals, domestic animals, wildlife and foxes submitted for rabies routine diagnosis between 1983 and 2008 and number of confirmed rabies for each category. High disease prevalences (% pos) in wildlife and foxes over the entire observation period clearly demonstrate the sylvatic nature of the rabies epidemic*

Year	Total	Thereof rabies positive	Domestic animals	Thereof rabies positive	% pos	Wildlife	Thereof rabies positive	% pos	Fox	Thereof rabies positive	% pos
1983	29 687	10 487	10 732	2018	19.2	18 888	8469	80.8	8653	7299	69.6
1984	29 608	9909	10 387	1728	17.4	19 171	8181	82.6	8551	7062	71.3
1985	28 180	8698	8987	1508	17.3	19 162	7190	82.7	7755	6276	72.2
1986	25 566	6679	7880	1107	16.6	17 636	5572	83.4	6509	4797	71.8
1987	23 534	5482	7480	793	14.5	15 989	4689	85.5	5684	4163	75.9
1988	26 742	4950	9089	934	18.9	17 573	4016	81.1	5567	3533	71.4
1989	34 575	6830	12 182	1237	18.1	22 302	5593	81.9	7686	4872	71.3
1990	32 423	5566	12 238	1095	19.7	20 112	4471	80.3	8600	3941	70.8
1991	26 221	3594	7834	626	17.4	17 072	2967	82.6	11 286	2663	74.1
1992	26 411	1422	7366	275	19.3	18 951	1147	80.7	14 841	1011	71.1
1993	25 198	839	5188	143	17.0	19 947	696	83.0	17 507	636	75.8
1994	19 234	1376	3233	235	17.1	15 962	1141	82.9	14 145	1044	75.9
1995	23 931	856	2349	155	18.1	21 545	701	81.9	20 308	636	74.3
1996	38 118	142	3003	31	21.8	34 760	111	78.2	32 654	107	75.4
1997	35 437	83	2739	8	9.6	32 540	75	90.4	30 424	74	89.2
1998	36 684	104	2450	8	7.7	34 091	96	92.3	32 172	86	82.7
1999	37 186	56	2286	12	21.4	34 721	44	78.6	32 769	37	66.1
2000	30 116	182	2037	16	8.8	27 889	166	91.2	26 217	150	82.4
2001	30 110	41	1643	3	7.3	28 297	38	92.7	26 811	35	85.4
2002	27 119	35	1362	2	5.7	25 498	33	94.3	23 976	24	68.6
2003	26 815	24	983		0	25 653	24	100	24 175	21	87.5
2004	26 752	34	935	1	2.9	25 576	33	97.1	24 054	27	79.4
2005	25 495	42	1136	1	2.4	24 123	41	97.6	21 997	39	92.9
2006	17 034	3	832		0	16 018	3	100	14 453	3	100
2007	17 530		703			16 642			14 848		
2008	14 832	1*	582	1*		14 086			12 561		
Total	714 538	67 434	125 636	11 936	17.1	584 204	55 497	82.3	454 203	48 536	79.2

* Imported dog rabies case from Croatia.

tive ORV campaigns. In contrast, in other federal states large-scale vaccination of coherent areas (Fig. 4) was implemented right from the beginning. Within 1 ½ year vaccination areas were constantly enlarged by overlapping previous areas until the entire territory was covered and subsequently vaccinated for at least five years (Schlüter and Müller, 1995; Selhorst et al., 2005).

By using an Area Index (AI) it was demonstrated that the two vaccination strategies applied clearly differed in success, as a direct correlation between the size of repeatedly vaccinated areas and the number of vaccination campaigns to be conducted until rabies elimination was achieved was evident. Large-scale vaccination clearly outperformed small-scale vaccination needing significantly less ORV and time (5–6 years, on average) to achieve freedom from disease (Fig. 4; Selhorst et al., 2005). Whenever there was a change of strategy to large-scale vaccination, e. g. as in Rhineland Palatinate, ORV was more successful and rabies elimination was achieved in less time, and hence, resulted in substantial cost savings (Selhorst et al., 2005).

Size of vaccination areas

The Ordinance on the Protection against Rabies dated 23 March 1991 (Federal Law Gazette I, 1168) stipulated a minimum size of vaccination areas of 5000 km². Since 1983, however, the overall size of the area under vaccination steadily increased and reached a peak at 215 805 km² (60.4% of Germany's total surface area) in 1991. From 1992 until 1996, the size of the area under vaccination remained relatively constant. Due to progressive rabies elimination at a local level from 1997 it steadily decreased until the cessation of the ORV campaigns in 2008 (Fig. 3). The total area ever covered at least once with vaccine baits in Germany between 1983 and 2008 comprised 315 148 km² (87.9%) (Fig. 4). Only in 4 of the 16 federal states ORV coverage did not encompass the entire territory, i. e. in North Rhine-Westphalia, Schleswig Holstein, Lower Saxony and Bavaria only 68.6%, 16.3%, 62.2% and 98.3%, respectively, of the territory was ever vaccinated (Fig. 4). The total number of vaccination campaigns conducted until rabies elimination varied considerably ranging from 1 to 50 ORV campaigns depending on the rabies incidence, the vaccination strategy (small- or large-scale vaccination), the prevailing rabies situation in neighbouring regions, and setbacks. A small area in the south-western part of Hesse comprising 738 km² was vaccinated twice annually from 1983 to 2008 (Fig. 4).

Requirements for rabies surveillance and monitoring of ORV campaigns

Requirements for rabies surveillance and monitoring of ORV campaigns i. e. bait-uptake (biomarker) and herd immunity (seroconversion), were first laid down in the national Ordinance on the Protection against Rabies dated 23 March 1991 (Federal Law Gazette I, 1168). Following international recommendations on rabies surveillance, a minimum of 8 foxes per 100 km² and year had to be investigated in rabies endemic areas (European Commission, 2002; World Health Organisation, 2005). If no case of rabies had been officially confirmed in an area for four years, the sample size could be reduced to a minimum of four foxes per 100 km² and year by focusing on indicator animals, e. g. animals showing abnormal behaviour suggestive of rabies, animals found dead, road kills and animals involved in human exposure (European Commission, 2002). Rabies routine diagnosis was conducted at regional veterinary laboratories of the federal states using internationally prescribed tests with the fluorescent antibody test (FAT) as a gold standard, and mouse inoculation test (MIT) and rabies tissue culture infection test (RTCIT) as confirmatory tests. Since the mid 1990s the MIT was replaced by RTCIT in all regional veterinary laboratories as recommended by WHO (Meslin et al., 1996).

For determination of bait-uptake (biomarker) and herd immunity (seroconversion) modified versions of histological (detection of tetracycline, TC) and serological standard techniques (Rapid Fluorescent Focus Inhibition Test – RFFIT), respectively, were applied (Cox and Schneider, 1976; Johnston et al., 1999; Linhart and Kenelly, 1967; Schaarschmidt et al., 2002; Stöhr et al., 1990a).

Sampling for monitoring of ORV campaigns aimed at detecting an estimated vaccination coverage of 70% (95% confidence interval [CI] with a desired accuracy of +/– 5%). To this end, 323 foxes within an area covering at least 5000 km² had to be tested per year for the presence of biomarker (TC) and virus neutralising antibodies (VNA). Sampling had to be randomly but evenly distributed over the entire vaccination area starting four weeks after distribution of vaccine baits in the field. In general, young foxes were to be excluded from testing, in particular in spring vaccination campaigns. Rabies virus isolates originating from vaccination areas were characterized using a panel of anti-N monoclonal antibodies and partial sequencing to distinguish vaccine from field rabies virus strains (European Commission, 2002; Schneider et al., 1985). In Saxony-Anhalt, reference zones for monitoring of ORV campaigns were established within the area under vaccination.

Rabies surveillance and monitoring of ORV campaigns

To follow international guidelines for rabies surveillance by just focusing on indicator animals proved to be difficult under field conditions. Often a pragmatic approach supplemented routine sampling with the addition of (healthy) hunted animals (hunting bag) to meet sample size requirements of WHO or EU (European Commission, 2002; World Health Organisation, 2005; World Health Organization, 1992). During 1983 and 2008 a total of 714 538 (81.7% wildlife, 18.3% domestic) animals were tested for rabies using FAT, of which 22 200 were confirmed by alternative tests (MIT; RTCIT). With 63.5% foxes accounted for the species most frequently tested followed by cats (8.4%), dogs (3.0%) and stone martens (2.7%) (Tab. 2). Of all animals tested during this period 67 434 (9.4%) were rabies positive in at least one of the prescribed tests, i. e. FAT, MIT, RTCIT, of which 71.9%, 2.3% and 3.1% were foxes, dogs, and cats, respectively. ORV in Germany started in the year with the highest rabies incidence ever reported. As a result of implementation of ORV in other federal states in subsequent years rabies cases declined steadily with an intermediate peak in 1989, the year when first field trials were launched in the eastern parts of the country. By 1996 the annual number of reported rabies cases was below 200 cases. Due to severe setbacks (see below) the rabies incidence slightly increased in 2000, but from 2001 never exceeded 50 cases and eventually disappeared in 2006 (Fig. 1). Since 1983 only one human rabies case after an encounter with a rabid fox had been reported from a yet unvaccinated area in East Germany in 1990.

Between 1983 and 2008, 9782 rabies virus isolates from vaccination areas were characterized either using a panel of anti-nucleoprotein (N) monoclonal antibodies or partial N sequencing. Because of intensive surveillance, four fox rabies cases were suspected to be caused by SAD vaccine virus of which two occurred in North Rhine-Westphalia in 2001 and 2004, and one each in Hesse and Rhineland Palatinate in 2002 and 2005, respectively (Müller et al., 2009), whilst characterization of the remaining 9778 isolates confirmed those RABVs from Germany clustered within the larger cosmopolitan group as described for other European virus isolates, e. g. western European group (WE), Central European (CE) and Eastern European group (EE) (Bourhy et al., 1999). Using standard rabies diagnostic tools (FAT), only two of the four vaccine-associated cases were identified as rabies cases. For two of these cases laboratory errors or contamination could not be excluded. No vaccine associated case had any epidemiological relevance for the elimination of rabies in Germany (Müller et al., 2009).

Bait-uptake and herd immunity in red foxes in ORV areas depend on many factors including bait-density, attractiveness of baits, fox density and its spatial distribution, food availability, weather conditions, health conditions as well as the population densities of bait competitors (Müller and Schlüter, 1998). Hence, bait-uptake and herd immunity rates of foxes obtained at a local level showed considerable temporal and spatial differences. Germany was the only European country abandoning the use of TC as a biomarker in vaccine baits in 1998 because of food law requirements in association with the consumption of game meat (wild boar) from vaccination areas (Schaarschmidt et al., 2002). Hence, data on bait uptake are only available for the time period 1983–1998. In early studies, on average, 58.1% and 76.9% of 14 118 and 17 317 control foxes originating from vaccination areas covered with SAD P5/88 and SAD B19 vaccine baits, respectively, tested TC-positive

TABLE 3: *Herd immunity in foxes based on virus neutralizing antibodies (VNA > 0.5 IU/ml) from vaccination areas in six Federal States between 2002 and 2007*

	2002		2003		2004		2005		2006		2007	
Federal state	N	pos. in %	N	pos. in %	N	pos. in %	N	pos. in %	N	pos. in %	N	pos. in %
North Rhine-Westphalia	957	49.01	297	59.93	668	50						
Baden-Württemberg	356	55.9	506	62.85	688	60.03	1509	52.95	1200	50	862	50
Hesse	217	42.86	380	57.89	262	63.74	230	51.74			457	33.04
Bavaria	349	46.13	348	33.91	323	52.94	528	42.99	246	52.03	129	48.06
Saxony	1106	67.99	1520	56.97	948	56.96	608	42.93				
Rhineland Palatinate							387	47.03	618	48.87	712	34.97
Total	2985	56.08	3051	55.72	2889	56.25	2875	48.9	1446	50.35	1448	44.48

(Stöhr et al., 1994; Vos et al., 2000a). Based on data sets of the national rabies database, of the 77 675 foxes submitted nationwide for biomarker detection between 1990 until 1998, 60% were TC-positive with variation at the local level. In Saxony for example, bait-uptake rates were shown to range between 78% and 86%, on average (Schaarschmidt et al., 2002).

The collection of serum samples from foxes under field conditions was problematic, both in terms of quantity and quality making it impossible to meet the high sample size as required by national legislation. Night shooting as practiced in France turned out to be impracticable in Germany (Bruyere et al., 2000). Nevertheless, 65.7% of 2508 fox sera investigated from field trial areas in East Germany between 1989 and 1991 had virus neutralising antibodies (VNA) (Stöhr et al., 1994). Of the 71 365 samples tested between 1990–1998, 60% had VNAs. One problem associated with serology was the use of different cut-offs at a national and international level which made comparison and interpretation of results difficult. Only after the mid 1990s standardised protocols were accepted. In Saxony, between 1992–2000 a total of 11 645 fox sera were tested during monitoring of ORV campaigns, of which 71–89% and 44–66% showed virus neutralizing antibodies for the years 1992–1996 and 1997–2000, respectively (Schaarschmidt et al., 2002). In the final phase of rabies elimination (2002–2007) herd immunity (titres > 0.5 IU/ml) in foxes from 6 different vaccination areas in Germany ranged between 33% and 68%, on average, at the time (Tab. 3).

Specifics of rabies elimination in Germany

Exchange of information and experience

Separation of the two German states prevented a uniform nationwide approach for reporting and collection of rabies and related data. In 1977, the first rabies database was set up in West Germany as part of a Europewide computerized rabies database established at the WHO Collaborating Centre for Rabies Surveillance and Research, Tübingen, encompassing monthly reported cumulative positive rabies cases at a municipality level. In East Germany, monthly electronic collection of rabies and ORV monitoring data based on individual data sets for any animal investigated started in 1989 after standard software was developed and provided to regional veterinary laboratories (Müller et al., 1993a). In 1994, the two separate databases were merged into a nationwide database to allow more sophisticated assessments of ORV campaigns.

For coordinating ORV campaigns and providing a national platform for exchange of information and experience among federal states a total of 14 Rabies-roundtable meetings were held during 1983 and 2008 under the auspices of the NRL for Rabies at the FLI (formerly BFAV). Besides general assessments of implemented ORV programmes and the prevailing rabies situation, legislative issues, practical aspects, strategic and scientific issues of future ORV campaigns in the federal states, harmonisation and standardisation of rabies diagnostics and reporting as well as setbacks were discussed, and recommendations for optimization and improvement of ORV programmes given. At an international level, next to periodic participation at informal WHO meetings on rabies control for Western and Eastern European countries, since the late 1990s regular trilateral meetings with veterinary authorities from Poland and The Czech Republic had been initiated to co-ordinate cross-border activities in the triangle border area with the two neighbouring countries (Schaarschmidt et al., 2002).

General causes for setbacks

Since Germany was the first country to start with large-scale ORV campaigns appropriate tools had to be developed from scratch. These pioneering developments proved favourable in subsequent rabies vaccination campaigns in other European countries (European Commission, 2002). Furthermore, the rabies situation in Germany was rather unique with the whole territory and almost all neighbouring countries infected. Thus, Germany (as subsequently other European countries) had to face several setbacks (Schlüter and Müller, 1995; Stöhr and Meslin, 1996), resulting in delay in rabies elimination at a local level, especially in the final phase of elimination. Disease managers often incorrectly attributed these problems to vaccine and bait, e. g. the efficacy and temperature stability of vaccines, and attractiveness of baits. In fact, reasons for setbacks were multifaceted including (i) over-optimistic interpretation of the initial success, which led to premature reduction of vaccination areas or premature declaration of areas as being "rabies-free" often followed by resurgence of the disease, (ii) missing cross-border activities, (iii) increasing fox densities, (iv) lack of adequate long-term planning and funding, (v) ignorance of principles in rabies control, (vi) missing complementary measures, e. g. manual bait distribution, hunting, (vii) inadequate bait distribution, (viii) insufficient epidemiological analysis, (ix) other disease priorities, (x) inadequate rabies surveillance, (xi) missing exchange of information, (xii) decreasing awareness, (xiii) deficient cold-chain for vaccines and (xiv) insufficient chains of command (Müller and Selhorst, 2007; Pastoret et al., 2004; Rupprecht et al., 2008; Selhorst et al., 2006). Moreover, the direct responsibility of federal states for animal disease control made it sometimes difficult to establish a common strategy at a national level which considerably prolonged rabies elimination in comparison with other European countries.

The complicated final phase of elimination

The final phase of rabies elimination in Germany proved particularly difficult. During 2000–2008 rabies persisted in a few separated residual foci in five federal states (Fig. 1). These foci were characterized by either low-level persistence of rabies, a temporal increase in rabies cases at a local level (Saxony, North Rhine-Westphalia, Hesse, Bavaria) or by rapid spread and re-infection of rabies free areas (Rhineland Palatinate). While the rabies situation in Saxony in 2000 reflected a classical cross-border problem due to infection pressure from adjacent areas in the Czech Republic and Poland, rabies persistence in the Ruhr District (North Rhine-Westphalia) an area with the highest density of urban settlements in Europe posed a challenge for rabies elimination. Optimization and adaptation of the vaccination strategy in Bavaria and North Rhine-Westphalia considering the peculiar topographical features, improved aerial and manual bait distribution and resulted in elimination of rabies in those regions by 2001 (Müller et al., 2005; Schaarschmidt et al., 2002). A far bigger problem was the persistence of rabies in high density urban settlement areas in the southernmost part of Hesse despite intensive large-scale vaccination. Due to suboptimal vaccination rabies spread further northwards and southwards at a low level resulting in a re-infection of adjacent areas in Baden-Wuerttemberg and Rhineland-Palatinate at the end of 2004 and the beginning of 2005, respectively. The re-emergence of rabies after six years of absence in Rhineland-Palatinate and its rapid spread was regarded as a worst case scenario (Müller et al., 2005). Corrective actions were implemented aiming at rapid disease elimination. Considering EU recommendations, in 2005 an improved and consistent ORV strategy was applied. Among a number of reinforced measures the core of the strategy was distributing baits in 6-week intervals (Müller et al., 2005), resulting in rabies elimination in February 2006. Two years later, in 2008 ORV ceased and a rabies free status was achieved according to OIE criteria (Anonym, 2008; Office International des Epizooties, 2008).

ORV costs and recoveries from EU

Direct and indirect costs were associated with rabies control, i. e. ORV. Direct costs referred to costs for the purchase and distribution of vaccine baits including transportation, storage and other costs (information of the public, warning signs, etc.). At a federal state level, indirect costs included staff salaries for regional veterinary laboratories and public authorities, costs for diagnostic tests as well as financial incentives for hunters for expense allowance and submission of samples for enhanced surveillance. A cost analysis of ORV campaigns in Germany for the period 1986 to 1996 revealed that the total costs per bait distributed predominantly amounted to costs for the vaccine bait (market-based price), followed by costs for distribution, logistics, e. g. storage and transportation (Selhorst and Schlüter, 1997). Recent costs analysis showed that for calculation of direct costs, a simple mathematical, linear relationship between the costs (c) on one hand and the number of baits distributed (n) and the area covered given in km^2 (a) could be set up: c[euro] = 0.82 euro*n + 2.01 euro*a. Hence, from start in 1983 to cessation in 2008, total direct costs for ORV in Germany amounted to approximately 80 million euro (Selhorst, unpublished). The sigmoid shape of the cumulated cost mainly resulted from the temporal dynamics of the total area under vaccination, which peaked in 1991 and remained at a high level until 1996 (Fig. 3). However, since in the beginning of ORV bait distribution had been exclusively performed by hand the calculated costs are slightly underestimated. Interestingly, to reduce the number of rabies cases by 90% required only 40% of direct costs, whereas 60% of financial resources were spent in the final phase of elimination (Fig. 5).

An assessment of indirect costs for diagnostic tests with regard to rabies surveillance and monitoring of ORV campaigns as part of the German eradication program is difficult, as fees for diagnostic tests varied both between federal states and over time, and because of the transition from D-mark to euro in 2002. Based on the number of specimens included in the rabies database and today's' average prices (2010) of 21.5 euro and 70 euro for FAT and confirmatory tests (RTCIT), respectively, the estimated costs for rabies surveillance for the time period 1983–2009 would amount to 16 917 000 euro. If 14.05 euro and 8.2 euro are taken as basis, the estimated costs for serological investigations using RFFIT (1990–2009) and bait-uptake (TC-detection, 1990–1999) would total approximately 1 210 000 euro and 637 000 euro, respectively. Costs for characterisation of rabies to distinguish vaccine from field virus strains from vaccination areas can be put at 407 000 euro. However, these costs need careful interpretation and are likely slightly underestimated as data of the first field trials could not be included. Also, other indirect costs associated with the control of the disease may not be reflected.

Based on Commission Decisions 89/455/EC and 90/424/EC Germany received 50% reimbursement of costs for national ORV campaigns including costs for purchase of vaccine baits and bait distribution for the years 1989–2008 to the amount of 33 384 000 euro. Recoveries for diagnostic investigations for rabies surveillance and monitoring of ORV campaigns for the years 2007–2009 accounted to 573 500 euro. Not only MS but also neighbouring non-EU countries with endemic rabies could benefit from co-financing by the EU provided a comparable rabies eradication programme was in place (Freuling et al., 2008b). This enabled Austria (1989–1992), the former GDR and Czechoslovakia (1989–1990) to claim recoveries for costs of ORV campaigns in adjacent regions from the EU via the German Ministry of Food, Agriculture and Forestry (89/455/EC). Due to modifications and amendments of co-financing as laid down in Commission Decision 90/424/EC, ORV in neighbouring none-EU countries could only be co-financed if expenses incurred in the adjacent MS. Hence, from 1997 to 2003 Germany was the only MS having allocated funds via national budgets to 50% for ORV campaigns in 100 km wide vaccination belts along common borders in the Czech Republic and Poland. Those costs amounted to an additional 4 131 650 euro of which 50% were later reimbursed by the EU. Hence, the EU and Germany each paid 25% of the total costs for those countries.

In total, between 1983 and 2009 approximately 100 million euro were spent for vaccine baits, rabies surveillance and monitoring of ORV campaigns of which approximately 37 million euro were covered by the EU.

Future prospect

Germany has achieved a rabies free status after intensive efforts. Currently, all measures are directed towards the maintenance of a rabies free status by avoiding reintroduction of the disease. Re-introduction of rabies through rabies infected pets from foreign countries in which rabies is endemic, is prevented by the pet travel scheme. Regulation 998/2003 EEC regulates the non-commercial movement of pets between member states, as well as from listed and non-listed third countries into the EU (European Community, 2003). Although this regulation is effective, between 2001 and 2010 several rabies-infected pets were illegally imported to Europe including Germany (Johnson et al., 2011). In Germany, two cases of imported rabies occurred in 2009 and 2010, respectively. Neither of those caused secondary rabies infections in animals or humans and therefore, did not change the rabies status of the country. Considering that all neighbouring countries are virtually free from rabies reintroduction of fox rabies appears unlikely but cannot be completely excluded. Therefore, risk-based rabies surveillance considering new scientific findings and a high level of vigilance has to be maintained at all levels to allow rapid detection of the disease and to prevent human cases (Cliquet et al., 2010; Thulke et al., 2009).

To be prepared for an emergency situation the establishment of a national bank of oral rabies vaccine baits for an immediate counteraction, similar to foot-and-mouth disease, is currently being planned.

Despite freedom from classical rabies caused by RABV, rabies as a disease will remain present in Germany since indigenous bats are reservoirs for bat-associated lyssaviruses, e. g. European bat lyssavirus type 1 and 2 (EBLV-1 and 2) and Bokeloh Bat Lyssavirus (BBLV) (Freuling et al., 2008a; Freuling et al., 2011; Müller et al., 2007a).

Conclusion

Elimination of fox rabies is a milestone in animal disease and zoonosis control in wildlife both at a national and international level thanks to pioneering spirit and work. Germany has played a substantial role in the development of oral rabies virus vaccines and set standards for practical proceedings for large-scale implementation of ORV in Europe. As a result, ORV has been developed into a modern and sophisticated method of disease control in wildlife and has served as a blueprint for the control of classical swine fever in wild boar. Success requires long-term planning, a consistent vaccination strategy and coordination beyond administrative borders. With an estimated 100 million euro elimination of fox rabies using ORV was one of the most cost-efficient animal disease control programmes in Germany. Nevertheless, rabies elimination in Germany took longer than in other Western European countries for reasons mentioned above. With hindsight, a common strategy at a national level from the start could have resulted in quicker rabies elimination at lower costs (Fig. 5).

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Conflict of interest: Adriaan Vos is employed by IDT Biologika GmbH, the manufacturer of the oral rabies virus vaccines used.

References

Anonym (1974a): Weisung Nr. 4 zur Tierseuchenverordnung – Verhütung und Bekämpfung der Tollwut bei Haustieren – vom 24.10.1974. (ed. Ministerium für Land-, Forst- und Nahrungsgüterwirtschaft).

Anonym (1974b): Weisung Nr. 5 zur Tierseuchenverordnung – Verhütung und Bekämpfung der Tollwut bei Wild – vom 24.10.1974. (ed. Ministerium für Land-, Forst- und Nahrungsgüterwirtschaft).

Anonym (1977): National Ordinance on the Protection against Rabies (Rabies Ordinance) dated 11 March 1977. Federal Law Gazette I444.

Anonym (1880): Ordinance concerning the Defense and Rejection of Livestock Diseases as of 23. June 1880. Reichsgesetzblatt 153.

Anonym (1989): Entscheidung des Rates vom 24. Juli 1989 vom 24. Juli 1989 – über eine Gemeinschaftsmaßnahme zur Aufstellung von Pilotprogrammen zur Tilgung oder Verhütung der Tollwut. Amtsblatt der Europäischen Gemeinschaften.

Anonym (2008): Austria and Germany declared "free from terrestrial rabies". Rabies Bull Eur 32: 7.

Aubert A (1992): Epidemiology of fox rabies. In: Bögel K, Meslin FX, Kaplan MM (eds.) Wildlife Rabies Control. Wells Medical Ltd., Kent, 9–18.

Baer GM, Abelseth MK, Debbie JG (1971): Oral vaccination of foxes against rabies. Am J Epidemiol 93: 487–490.

Black JG, Lawson KF (1973): Further studies of sylvatic rabies in the fox (*vulpes vulpes*). Vaccination by the oral route. Can Vet J 14: 206–211.

Breitenmoser U, Müller U (1997): How to do the wrong thing with the highest possible precision – a reflection on the use of GPS in rabies vaccination campaigns. Rabies Bull Eur 21: 11–13.

Breitenmoser U (2000): Tollwutfreiheit der Schweiz nach 30 Jahren Fuchstollwut. Schweiz Arch Tierheilk 142: 423–429.

Breitenmoser U, Müller U, Kappeler A, Zanoni R (2000): Die Endphase der Tollwut in der Schweiz. Schweiz Arch Tierheilkd 142: 447–454.

Bourhy H, Kissi B, Audry L, Smreczak M, Sadkowska-Todys M, Kulonen K, Tordo N, Zmudzinski JF, Holmes EC (1999): Ecology and evolution of rabies virus in Europe. J Gen Virol 80: 2545–2557.

Bruyere V, Vuillaume P, Cliquet F, Aubert M (2000): Oral rabies vaccination of foxes with one or two delayed distributions of SAG2 baits during the spring. Vet Res 31: 339–345.

Cliquet F, Aubert M (2004): Elimination of terrestrial rabies in western european countries. In: Schudel A, Lombard M (eds.) Control of infectious diseases by vaccination. Karger, Basel, 185–204.

Cliquet F, Freuling C, Smreczak M, van der Poel WHM, Horton DL, Fooks AR, Robardet E, Picard-Meyer E, Müller T (2010): Development of harmonised schemes for monitoring and reporting of rabies in animals in the European Union. Scientific Report submitted to EFSA (Q-2010-00078).

Cox JH, Schneider LG (1976): Prophylactic Immunization of Humans Against Rabies by Intradermal Inoculation of Human Diploid Cell Culture Vaccine. J Clin Microbiol 3: 96–101.

Debbie JG, Andrulonis JA, Abelseth MK (1972): Rabies antibody determination by immunofluorescence in tissue culture. Infect Immun 5: 902–904.

Dietzgen RG, Calisher CH, Kurath G, Kuzmin IV, Rodriguez LL, Stone DM (2011): Family Rhabdoviridae. In: King AMQ, Adams MJ, Carstens EB, Lefkowitz EJ (eds.) Virus taxonomy: classification and nomenclature of viruses. Ninth Report of the International Committee on Taxonomy of Viruses. Elsevier, San Diego.

European Commission (2002): The oral vaccination of foxes against rabies. Report of the Scientific Committee on Animal Health and Animal Welfare Adopted on 23 October 2002.

European Community (2003): Regulation (EC) No 998/2003 of the European Parliament and of the Council of 26 May 2003 on the animal health requirements applicable to the non-commercial movement of pet animals and amending Council Directive 92/65/EEC. Official Journal of the European Communities L 146: 1–9.

Freuling C, Grossmann E, Conraths F, Schameitat A, Kliemt J, Auer E, Greiser-Wilke I, Muller T (2008a): First isolation of EBLV-2 in Germany. Vet Microbiol 131: 26–34.

Freuling C, Selhorst T, Batza HJ, Müller T (2008b): The financial challenge of keeping a large region rabies-free – the EU example. Dev Biol (Basel) 131: 273–282.

Freuling CM, Beer M, Conraths FJ, Finke S, Hoffmann B, Keller B, Kliemt J, Mettenleiter TC, Muhlbach E, Teifke JP, Wohlsein P, Muller T (2011): Novel Lyssavirus in Natterer's Bat, Germany. Emerg Infect Dis 17: 1519–1522.

Frost JW, Wachendörfer G, Gutmann B, Dingeldein W, Schneider LG (1985): Erste Erfahrungen mit der oralen Immunisierung von Füchsen gegen Tollwut in Hessen. Berlin Münch Tierärztl Wochenschr 98: 279–281.

Gschwender P, Holzhofer E, Mürke H, Schuster P, Böhme H (1996): Einsatz des vollautomatischen Impfköderabwurfsystems SURVIS. Amtstierärztl Dienst Lebensmittelkontrolle 3: 255–258.

Johnson N, Freuling C, Horton D, Müller T, Fooks AR (2011): Imported rabies, European Union and Switzerland, 2001–2010. Emerg Infect Dis 17: 753–754.

Johnston DH, Joachim DG, Bachmann P, Kardong K, Stewart RB, Dix L, Strickland M, Watt I (1999): Aging furbearers using tooth structure and biomarkers. In: Novak MJ, Baker JA, Obbard ME, Malloch B (eds.) Wild furbearer management and conservation in North America. 228–243.

Kintscher M, Bernhard J, Lemke I (1990): Untersuchungen zur Unschädlichkeit, epizootiologischen Unbedenklichkeit und Wirksamkeit des Tollwutimpfstammes SAD/Potsdam 5/88. Monatsh Veterinarmed 45: 81–84.

Kuzmin IV, Mayer AE, Niezgoda M, Markotter W, Agwanda B, Breiman RF, Rupprecht CE (2010): Shimoni bat virus, a new representative of the Lyssavirus genus. Virus Res 149: 197–210.

Linhart SB, Kenelly JJ (1967): Fluorescent bone labeling of coyotes with Demethylchlortetracycline. J Wildl Manage 31: 317–321.

MacInnes CD, Tinline RR, Voigt DR, Broekhoven LH, Rosatte RR (1988): Planning for rabies control in Ontario. Rev Infect Dis 10: 665–669.

Manz D (1979): Untersuchungen zur Nahrungsspeicherung des Fuchses (*Vulpes vulpes* L.) und zur Auswirkung dieses Verhaltens auf die perorale Vakzination gegen Tollwut. Berlin Münch Tierärztl Wochenschr 92: 376–379.

Matouch O, Vitasek J (2005): Elimination of rabies in the Czech Republic by oral vaccination of foxes. Rabies Bull Eur 29: 10–15.

Meslin FX, Kaplan MM, Koprowsk H (1996): Laboratory techniques in rabies. In: (eds.)World Health Organization, Geneva, Switzerland, 157–170.

Müller T, Schröder R, Klöß D (1993a): Computerprogramme combining rabies surveillance and follow-up investigations in connection with oral vaccination of foxes against rabies. Rabies Bull Eur 17: 11–14.

Müller T, Stöhr K, Loepelmann H, Neubert A, Schuster P, Karge E (1993b): Testung eines neuen Köders für die orale Immunisierung des Rotfuchses (*Vulpes vulpes*) gegen Tollwut Berlin Münch Tierärztl Wochenschr 106: 41–46.

Müller T, Stöhr K, Teuffert J, Stöhr P (1993c): Erfahrungen mit der Flugzeugausbringung von Ködern zur oralen Immunisierung der Füchse gegen Tollwut in Ostdeutschland. Dtsch Tierärztl Wochenschr 100: 169–208.

Müller T, Schlüter H (1998): Oral immunization of red foxes (*Vulpes vulpes* L) in Europe. A review. Etlik veteriner mikrobiyoloji Dergisi 9: 35–59.

Müller W (2000): Review of rabies case data in Europe to the WHO Collaborating Centre Tübingen from 1977 to 2000. Rabies Bull Eur 24: 11–19.

Müller T, Vos A, Selhorst T, Stiebling U, Tackmann K, Schuster P, Neubert A, Conraths FJ, Schlüter H (2001): Is it possible to orally vaccinate juvenile red foxes against rabies in spring campaigns? J Wildl Dis 37: 791–797.

Müller W, Cox J, Müller T (2004): Rabies in Germany, Denmark and Austria. In: King AA, Fooks AR, Aubert M, Wandeler AI (eds.) Historical perspective of rabies in Europe and the Mediterranean Basin. OIE, Paris, 79–91.

Müller T, Selhorst T, Potzsch C (2005): Fox rabies in Germany – an update. Euro Surveill 10: 229–231.

Müller T, Johnson N, Freuling CM, Fooks AR, Selhorst T, Vos A (2007): Epidemiology of bat rabies in Germany. Arch Virol 152: 273–288.

Müller T, Selhorst T (2007): Principles in rabies eradication. Meeting on Enhancing Rabies Eradication in the EU: International Cooperation organized by the Finnish presidency of the EU and the EU Commission. Helsinki, 7–8 December 2006.

Müller T, Bätza HJ, Beckert A, Bunzenthal C, Cox J, Freuling C, Fooks A, Frost J, Geue L, Hoeflechner A, Marston D, Neubert A, Neubert L, Revilla-Fernandez S, Vanek E, Vos A, Wodak E, Zimmer K, Mettenleiter T (2009): Analysis of vaccine-virus-associated rabies cases in red foxes (*Vulpes vulpes*) after oral rabies vaccination campaigns in Germany and Austria. Arch Virol 154: 1081–1091.

Neubert A, Schuster P, Müller T, Vos A, Pommerening E (2001): Immunogenicity and efficacy of the oral rabies vaccine SAD B19 in foxes. J Vet Med B Infect Dis Vet Public Health 48: 179–183.

Office International des Epizooties (2008): Rabies. In: (eds.) OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. OIE, Paris, 307–308.

Pastoret PP, Kappeler A, Aubert M (2004): European rabies control and its history. In: King AA, Fooks AR, Aubert M, Wandeler AI (eds.) Historical perspective of rabies in Europe and the Mediterranean Basin. OIE (World Organisation for Animal Health), Paris, 337–350.

Rupprecht CE, Barrett J, Briggs D, Cliquet F, Fooks AR, Lumlertdacha B, Meslin FX, Müller T, Nel LH, Schneider C, Tordo N, Wandeler AI (2008): Can rabies be eradicated? Dev Biol (Basel) 131: 95–121.

Schaarschmidt U, Müller T, Albert G, Muluneh A, Cox J, Selhorst T, Schlüter H (2002): Erfahrungen mit der Begleitdiagnostik zur oralen Immunisierung der Füchse in Sachsen unter besonderer Berücksichtigung einer standardisierten Tollwutserologie. Dtsch Tierärztl Wochenschr 109: 219–225.

Schlüter H, Müller T (1995): Tollwutbekämpfung in Deutschland. Ergebnisse und Schlußfolgerungen aus über 10-jähriger Bekämpfung. Tierarztl Umsch 50: 748–758.

Schneider LG (1990): Der Einfluß der oralen Immunisierung der Füchse auf die Epidemiologie der Tollwut. In Fuchs-Symposium, 145–163. Koblenz, 2.–3. März 1990: Schriften des Arbeitskreises Wildbiologie an der Justus-Liebig-Universität Gießen e.V.

Schneider LG (1989): Der Feldversuch zur oralen Immunisierung von Füchsen gegen die Tollwut. Jagd und Tollwut, München, 1–16.

Schneider LG, Cox JH (1983): A Field Trial for the Oral Immunization of Foxes Against Rabies in the Federal-Republic of Germany. 1. Safety, Efficacy and Stability of the Sad-B19 Vaccine. Tierärztl Umsch 38: 315–324.

Schneider LG (1984): Feldversuch zur oralen Immunisierung von Füchsen gegen die Tollwut in der Bundesrepublik Deutschland. In: Tagung der Fachgruppe Tierseuchenrecht: 25–53. Giessen, 14.–15.06.84: Deutsche Veterinärmedizinische Gesellschaft.

Schneider LG, Barnard BJH, Schneider HP, Odegaard OA, Mueller J, Selimov M, Cox JH, Wandeler AI, Blancou J, Meyer S (1985): Application of monoclonal antibodies for epidemiological investigations and oral vaccination studies. In: Kuwert E, Merieux C (eds.) Rabies in the tropics. Springer Verlag, Berlin, 47–59.

Schneider LG, Cox JH, Müller WW, Hohnsbeen KP (1987): Der Feldversuch zur oralen Immunisierung von Füchsen gegen die Tollwut in der Bundesrepublik Deutschland – eine Zwischenbilanz. Tierärztl Umsch 3: 184–198.

Selhorst T, Schlüter H (1997): Cost-benefit analysis of the oral immunization strategy for the control of rabies in fox populations. Epidemiol sante animale 31–32: 10.20.11–10.20.13.

Selhorst T, Müller T, Schwermer HP, Ziller M, Schlüter H (2005): Use of an area index to retrospectively analyze the elimination of fox rabies in European Countries. Environ Manage 35: 292–302.

Selhorst T, Müller T, Bätza HJ (2006): Epidemiological analysis of setbacks in oral vaccination in the final stage of fox rabies elimination in densely populated areas in Germany. In: Dodet B, Schudel A, Pastoret PP, Lombard M (eds.) Developments in biologicals. Karger, Basel, 127–132.

Sinnecker H, Apitzsch L, Berndt D, Schrader C, Gogolin J, Egert J (1990): Die Entwicklung des Tollwutlebendimpfvirus SAD/Potsdam 5/88 zur oralen Fuchsimpfung sowie seine Charakterisierung am Mausmodell. Monatsh Veterinärmed 45: 77–78.

Steck F, Wandeler AI, Bichsel P, Capt S, Schneider LG (1982): Oral Immunisation of Foxes against Rabies. Zbl Vet Med B 29: 372–396.

Stöhr K, Gebauer R, Herold W, Hähn J, Pietel W, Kintscher M (1990a): Fluoreszenzmikroskopischer Nachweis von Oxytetracyclin in Knochen von Füchsen. Monatsh Veterinarmed 45: 88–92.

Stöhr K, Karge E, Gädt H, Kokles R, Ehrentraut W, Witt W, Fink HG (1990b): Orale Immunisierung freilebender Füchse gegen Tollwut – Vorbereitung und Durchführung der ersten Feldversuche in den ostdeutschen Bundesländern. Monatsh Veterinarmed 45: 782–786.

Stöhr K, Karge E, Loepelmann F, Gebauer R, Dedek J, Hähn J (1990c): Die Entwicklung des Impfköders für die orale Immunisierung freilebender Füchse gegen Tollwut. Monatsh Veterinärmed 45: 165–169.

Stöhr K, Meslin FX (1996): Progress and setbacks in the oral immunisation of foxes against rabies in Europe. Vet Rec July 13: 32–35.

Stöhr K, Stöhr P, Müller T (1994): The Results and Observations of the Oral Vaccination of Foxes Against Rabies in Eastern Germany. Tierärztl Umsch 49: 203–211.

Taylor D (1976): Rabies: Epizootic aspects; diagnosis; Vaccines; notes for guidance; official policy – Epizootic aspects. Vet Rec 99: 157–160.

Thulke H, Eisinger D, Freuling C, Frohlich A, Globig A, Grimm V, Muller T, Selhorst T, Staubach C, Zips S (2009): Situation-based surveillance: adapting investigations to actual epidemic situations. J Wildl Dis 45: 1089–1103.

Vos A, Neubert A, Aylan O, Schuster P, Pommerening E, Müller T, Chivatsi DC (1999): An update on safety studies of SAD B 19 rabies virus vaccine in target and non-target species. Epidemiol Infect 123: 165–175.

Vos A, Müller T, Schuster P, Schlüter H, Neubert A (2000a): Oral vaccination of foxes against rabies with SAD B19 in Europe, 1983–1998: A review. Vet Bull 70: 1–6.

Vos A, Müller T, Tackmann K, Schuster P, Neubert A (2000b): Studies on the resudual pathogenicity of SAD P5/88 rabies vaccine in small mammals. Infect Dis Rev 2: 128–132.

Vos A, Mührke HH, Holzhofer E, Gschwendner P, Schuster P (2001a): A satellite navigated and computer supported fully automatic system for distributing oral vaccine-baits against rabies: SURVIS 2001. In Proceedings of the XIIth International Meeting on Advances in Rabies Research and Control in the Americas. Peterborough, Canada, 12.–16. November 2001.

Vos A, Müller T, Selhorst T, Schuster P, Neubert A, Schlüter H (2001b): Optimising spring oral vaccination campaigns of foxes against rabies. Dtsch Tierärztl Wochenschr 108: 55–59.

Vos A, Sutor A, Selhorst T, Pötzsch C, Staubach C, Müller T (2004): The spatial and temporal disappearance of different oral rabies vaccine baits. Berl Münch Tierärztl Wochenschr 117: 360–366.

Wachendörfer G, Frost J (1992): Epidemiology of fox rabies: a review. In: Bögel K, Meslin FX, Kaplan MM (eds.) Wildlife Rabies Control. Wells Medical Ltd., Kent, 19–31.

Wandeler AI, Capt S, Kappeler A, Hauser R (1988): Oral Immunization of Wildlife Against Rabies: Concept and First Field Experiments. Rev Infect Dis 10: 649–653.

World Health Organisation (2005): Expert Consultation on Rabies, First report. World Health Organ Tech Rep Ser 931: 1–121.

World Health Organization (1992): Expert Committee on rabies : 8th report. In: (eds.) World Health Organ Tech Rep Ser. WHO, Geneva, 1–84.

Zanoni RG, Kappeler A, Müller UM, Müller C, Wandeler AI, Breitenmoser U (2000): Rabies free status of Switzerland after 30 years of fox rabies. Schweiz Arch Tierheilkd 142: 423–429.

Address for corrspondence:
Dr. Thomas Müller
Institute of Epidemiology
Friedrich-Loeffler-Institut
Seestr. 55
16868 Wusterhausen
Germany
thomas.mueller@fli.bund.de