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RABIES

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This contribution will focus mainly on the epidemiology and the control of rabies in Europe and therefore my talk will be divided into three parts. The first part will be devoted mainly to the epidemiology of the disease, the second part will be devoted to a few items on the development of a recombinant virus in order to vaccinate foxes in the wild and the third part will be devoted to the present situation in Europe following fox vaccination. Just to remind you about rabies virus, it is a Lyssavirus and as you know, the virus can infect many different species. In fact you could say all mammals. Within those species only a few ones are what we call 'reservoirs' that maintain the virus. Most of the species that you see currently in Europe are dead end species, that means that they can be infected, they develop the disease but they do not maintain the infection. Therefore, in fact in Europe you have only two types of reservoir, both are wildlife because we have no more to face urban rabies linked to the dog; the first one being the fox, the second one being bats. It is well recognised now that there are several Lyssavirus genotypes. The most prevalent one and responsible for terrestrial rabies in Europe is type 1, but we also have in Europe two other types, five and six linked to bats. Firstly will focus on bat rabies. Lyssavirus ELB5 and ELB6 are linked to insectivorous bats. Compare that to Latin America where rabies is found in vampire bats. Here in Europe of course it is only insectivorous bats and what is striking is that from time to time we have infection in humans. There are several well recog- nised cases in Europe and recently it has been well documented in Denmark in sheep. So there is some interaction between aerial cycle and terrestrial animals. So this problem of aerial rabies will really be the most difficult to solve in the future. The second one, as already mentioned, is linked to the fox. It is a carnivore and contrary to what many people think, humans are not infected due to direct contact with foxes but through contact with infected domestic animals. For example rabid foxes can come into contact with cows and then may be transmission to human beings occur. The rationale of what I will talk about is that if you are able to control the disease within the reservoir species you will be able to control it within the other species such as cattle and man.

In France in 1998, terrestrial rabies was nearly already eliminated but you could still isolate one rabies virus from cat, from fox, from serotine bat and also they had an exotic introduction of a canine strain coming from Egypt. The situation in 1999 was that they had no more isolates originating in France but there was an exotic introduction through Brussels to France coming from Africa.

Coming back again to our main animal the fox, the main reservoir in Europe, humans are rarely directly at risk due to contact with foxes, but mainly through contact with cattle or cats, which had

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been exposed to bites by foxes.

I will now tell you about the development of recombinant vaccinia rabies virus. As you know vaccinia virus has been used to eradicate smallpox and it is used now as a vector for foreign immunogens and the foreign immunogen which was used is the glycoprotein from rabies virus. It has been known for years that the main immunogen of rabies virus is the transmembrane protein which is a glycoprotein. It is sufficient to induce protection in the animal. The only problem with this recombinant vaccine was the fact that it was a genetically modified virus and therefore people were afraid about the use of this kind of virus especially due to the fact that it had to be used in an eco-system rather than in an agro-system.

Therefore, we had to face two or let us say three main problems. The first one being the stability of the vaccine in the wild. This has been solved, due to the fact that we were using vaccinia virus as a vector which is a very stable virus. The second one is the fact that as far as rabies is concerned, there are many different species that could be involved. For example, in the USA, there are several wildlife reservoirs and therefore you must have a vaccine that can be used in different species. The last problem was the fact that if you want to vaccinate wildlife, you have only one way, that is, to use the oral route.

Coming back to the recombinant. The first step when developing the vaccine was to check for efficacy because it would have been useless to go into the wild with an ineffective vaccine. We did try to find out how long this vaccination should protect and therefore we did a survey of the mean age of fox population in Belgium. Ninety-five percent of foxes are under 2 years old and there- fore the only thing we had to do was to have a vaccine that could protect the foxes for at least 2 years. Those foxes are not living in Oxford; they are living in the wild, and therefore there is a big turnover in the population.

Some of the first steps were to look at efficacy and we could show that one shot of this vaccine by oral route could protect at least 2 years. The next step was to look at safety and we had to do many experiments on residual pathogenicity, horizontal transmission, gene stability, … The main step was to check, because it was not used in an agro-system but in an eco-system, for non-target species safety. We tested around 50 different species with always the same result: it was safe. The last species to be tested was chimpanzees to check if it was also safe for the species most related to man.

So after that, we had to find a way to give the vaccine to the foxes. A bait was devised which contained tetracycline which we used as a bio- marker and within the bait there was a plastic sachet containing the vaccine in a liquid form. Therefore, when the fox takes the bait and chews the plastic bag it is therefore vaccinated. Vaccination is induced locally and we have evidence that you require only one viral multiplication. This vaccine was first tested in Belgium in a small area where of course you have foxes, you have cattle and you have rabies, with conclusive results. Therefore, we could proceed and use it on a larger scale. The strategy we used for vaccine bait distribution was an uniform distribution at the beginning. Each bait used cost one U.S. dollar (one Euro, more or less) we distributed 15 – 20 vaccine baits per square kilometre either manually or by aerial dissemination and it was done twice a year. Why do you do it twice a year? Because as already mentioned you have a big turnover in fox population and very quickly the number of vaccinated foxes within the population may decrease and therefore you have to do it at least twice

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per year.

What is really important of course is cross-bor- der collaboration as there are always problems along the Border. We found that you must in- crease the immunisation rate according to the fox density. For instance if you have four foxes per square kilometre, you must have around 90% of foxes vaccinated. But in most cases we had around one to two foxes per square kilometre and therefore we had to reach only 80% coverage. And what is also important is the surveillance; you cannot do it without very strong and pro-ac- tive surveillance. First of all of course, you look at rabies incidence and also you try to find out your immunisation rate, both looking at tetracycline incorporation into fox bones and serological anal- ysis. What is even more important is the fact that your surveillance must be pro-active; you do not just wait until people come with infected foxes; you must go and shoot foxes in order to check if they are positive or negative.

The results show that if you can control rabies within the reservoir species, you will be able to control it in the other species which are dead end species, such as cattle and man. Cattle now are the most exposed domestic species to rabies and when we had the peak of rabies in 1989, we had as much as 162 cattle becoming rabid. We know for sure the number of rabid cattle; it is therefore an important indicator and the best way to know the real situation in the wild. Taking measures and controlling disease within wildlife has a positive effect on public health. We could reduce to nearly nil, the number of human post-exposure treatments in our country. In fact it is just a precautionary measure if we still vaccinate post- exposure because there had been no rabies for nearly 2 years now.

Another result of vaccination campaigns against rabies in foxes was the increase in fox population. This could be due to the fact that rabies was playing a role in its control. In other words, if you eliminate rabies you will have an increase in the fox population. The measures taken in a few European countries in the beginning have been extended to numerous other countries. The results show that compared to 1984 the situation has been quite improved in 1999. In 1999 only small pockets of rabies remain in Germany, in Czechoslovakia and in other Eastern countries but for the rest of Europe it is nearly clear and rabies is nearly eliminated from the main part of continental Europe. Four countries are going to be recognised as being free namely France, Belgium, Luxembourg and Austria.

The consequences of these results is the beneficial effect on public health. The main goal when vaccinating foxes is mainly to improve human health and domestic animal health not foxes health. Also as you know new regulations concerning quarantine within Europe have been set up. Now quarantine has been replaced by vaccination and serological testing before entering the UK. It is based on the fact that the situation is much improved within continental Europe and also due to the fact that if you look at the real numbers, the probability of introducing rabies to the UK, through dogs or cats, has always been low. First of all because, I did not mention this before, but you must take the virus biotypes into account. Each reservoir species for example foxes, has its own biotype of rabies virus which has special biological properties; rabies viruses are highly variable viruses. The worse case scenario being the introduction of rabies through a dog from France to the UK. If you look at the numbers, in fact in 1991 you had only in France 38 cases of rabies in dogs related to a population of about 10 million dogs in France at that time; it is a very simple calculation, you can show that in fact the risk to introduce rabies through dogs notwithstanding the fact that the virus has a different biology in dogs than in foxes, it is only once

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every 1.250 years if 1000 dogs were intro- duced each year and of course five times less if you introduce 5000 dogs.

To conclude I think that it has been shown both in Europe and in the USA. that using the recombinant vaccinia rabies virus for wildlife vaccination has beneficial effects on public health, domestic animal health and fox population. I think the next step for rabies will be to try to have efficacious vaccines to be given by oral route to dogs in order to prevent most of the human cases, where you have urban rabies. Unfortunately it will not only be a practical problem but also an economical problem.

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