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Dear Ms Reerink

Oostvaardersplassen: Immunocontraception of large grazers

I visited the Oostvaardersplassen together with people from the Veterinary Faculty of the University of Utrecht and a Dutch ecologist in 2010. I cannot claim to have expert knowledge of the reserve but I saw enough to formulate an opinion regarding the overpopulation of the reserve with especially horses, deer and cattle. I was also told about and shown photos of the effects of overpopulation has on mortalities, especially during the winter months as a result of starvation. Natural mortalities of old, sick and very young animals that are unable to take in sufficient feed during the winter season is a natural biological cycle. However, as a result of the sheer numbers of animals the mortalities are no longer natural. Certainly they can be largely avoided.

Over the past 10 years I have been approached either directly or indirectly, through Prof. Stout and Colenbrander, on a number of actions for my opinion on the matter and a possible solution. I responded each time that contraception of these species can be applied successfully. It seems that the advice I gave fell on deaf ears. I even offered to visit the site with interested parties together with Prof Stout to discuss implementation of contraception. The offer still stands, despite the fact that I come from a developing country, although my postgraduate training was achieved in Zurich (DrMedVet) and The Netherlands (PhD). On the other hand, in South Africa we have much more experience in handling and managing wildlife, which is effectively what you are dealing with in the Oostvaaderplassen, than Europeans have.

Porcine zona pellucida vaccine – wild horses and elephants

As you mentioned in your letter, immunocontraception using the porcine zona pellucida (pZP) vaccine has been successful for POPULATION CONTROL of two species in particular. These are wild horses in the USA and African elephants in South Africa. Prof Stout has summarised the work carried out with the pZP vaccine in horses extremely well. The data presented conclusively confirms that the pZP vaccine successfully controls reproduction of horses and is thus an effective population management tool for wild horses in the USA. In South Africa we carried out the first field trial on wild African elephants in the Kruger National Park in 1997 and showed that pZP is an effective at preventing pregnancies. From 2000 the first wild elephants were contracepted with pZP in a private game reserve. After four years we were able to show that the pZP vaccine is 100% effective at preventing pregnancy in treated cows (Delsink et al. 2007). From 2003 continuing through to today, more and more reserves, including 28 private game reserves, one national park (Addo Elephant Park) and 5 provincial reserves in the province of KwaZulu-Natal, have placed their elephants on population control using the pZP vaccine. In reserves with larger populations of elephant treatment of every cow during each round of vaccinations is not possible. However, the vaccine is effective even if only 85-90% of the population is treated. Today, our Laboratory manufactures and supplies >1000 doses of pZP vaccine annually for the treatment of ≈1000 cows in 34 game reserves in South Africa (Bertschinger et al. 2019).

International movement of pZP vaccine and recombinant ZP

The importation of pZP from either South Africa or the USA to The Netherlands is understandably prohibited as the vaccine is made from the ovaries of pigs that are slaughtered for human consumption. There is a very small chance that heat resistant pathogens could survive the manufacturing process. Despite the small chance of disease transmission the EU and many other countries will not allow importation of pZP vaccine. For this reason and because pZP production is labour-intensive and expensive, we decided to develop and test a recombinant zona pellucida (reZP) vaccine expressed in *Escherichia coli* bacteria. The synthesis was successful and has now been tested in mice, horses (Nolan et al. 2018; Nolan et al. 2019) and donkeys (French et al. 2020). The results showed that it is equally effective as the pZP vaccine as an immunocontraceptive. This vaccine is however not registered for use excepting for experimental purposes (we tested it in donkeys in the Caribbean). It would probably not be an option for use in the Oostvaardersplassen.

The GnRH vaccine Improvac (Zoetis Animal Health).

This is a vaccine that is registered for the immuno-castration of male piglets in South Africa and the EU which makes it easy to access for extra-label use. GnRH vaccines have two other advantages. They are effective in both sexes and in the female they cause anoestrus (fail to show an oestrous cycle), which is more physiological than animals that come on heat repeatedly (pZP immunocontraception). As an example

the mare (untreated), once she has foaled, will cycle once or twice, conceive and then remain in anoestrus until she foals down again 11 months later. How soon she conceives after foaling depends on body condition which is largely dependent on feed availability. So spending most of her reproductive life in anoestrus is natural for the mare. Animals that have a seasonal breeding pattern (includes the horse) would be similar. We have used Improvac in horses (mares and stallions) and African elephants (cows and bulls) successfully (Bertschinger and Lueders 2019).

In a horse study we injected 55 mares twice with 400 µg of the active vaccine 5 weeks apart. By Day 35 (day of the 2nd treatment) only 14.5 % of mares were still cyclic; the rest had entered anoestrus. By Day 70 all mares were in anoestrus (Botha et al. 2008). We continued to monitor the mares to establish when they started to cycle again and could theoretically be mated and conceive. The mean interval to the first cycle was 417.8 days with a range of 232–488 days (Schulman et al. 2012). This means that two injections 5 weeks apart were able to suppress mares coming into oestrus for a minimum of 232 days. Four younger mares had not yet cycled after 720 days. In practical terms, Improvac treatment at the beginning summer would have suppressed ovarian cycles (contracepted) for the entire seasonal breeding period and, for many mares, through the following season as well. These mares had ad lib access to feed throughout the year; contrary to the horses at the Oostvaardersplassen. The impact of two treatments in Oostvaarderplassen mares can be expected to last longer. Using a single annual booster would further prolong the effect.

The solution for Oostvaardersplassen?

This is clearly an animal welfare issue, particularly when the animals enter the winter period in the Oostvaardersplassen. Science has also shown that removal (WEGHALEN VAN DIEREN) of animals through translocation or culling (ruiming / AFSCHIETEN) simply decreases the population density and large herbivores respond with increased reproductive rate. The result – the more you remove, the more you have to keep removing (Bertschinger et al. 2008). Secondary effects are inbreeding which ultimately will result in reduced fitness and, of course, the effects on the habitat which, due to my lack of knowledge of European ecological systems I cannot comment on. I fail to understand why, in a first world country like the Netherlands, people are reluctant to use a tool (and probably the only one) that works and is considered to be ethically acceptable. Politics should play absolutely no role whatsoever in taking such a decision. If we in South Africa can treat wild elephants and indeed other wildlife species like lions with contraceptive agents, why not in the Oostvaardersplassen? It will be considerably easier to do so than finding and treating elephants and lions in game reserves that are 10-60 000 ha or larger.

The beginnings of elephant immunocontraception were difficult and progress was slow. Firstly the methodology had to be tested and developed and secondly there

was a lot of opposition which we overcame. For Oostvaardersplassen I would suggest that you start with small study involving between 50 and 100 mares that can be individually identified. These mares are treated twice as described above (we can supply the details) and monitored for a year. The number of foals born the following year is compared to foals born in the untreated population of mares. This initial study can be used to demonstrate the effect of the treatment to managers and politicians. What is there to lose? NOTHING! But, there is so much to gain. The most difficult part of the study will be to catch the mares and identify them. There are a few methods that can be used and have been applied in wildlife in South Africa. Following that remote delivery of vaccine for the booster can be used which does not require capture. Also, if the method is to be accepted and applied regularly, all treatments can be carried out remotely without capture.

Yours sincerely

Prof Henk Bertschinger