**Sporopollenin encapsulation to deliver oral immunocontraceptive vaccine to mammals**

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Good afternoon. My colleagues and I are based at the National Wildlife Management Centre in York. This is part of APHA, an executive agency of Defra. The main focus of our work is to provide solutions to prevent or mitigate the environmental and economic impact of wildlife.
We would like to offer a brief overview of our work on fertility control to manage human-wildlife conflict, talk about progress on oral contraceptives and present a study that we would like to conduct and that we believe has potential to revolutionize this field.
You may be aware of the environmental and economic impacts of wildlife that I have listed in this slide.
To resolve such conflicts we can use either lethal control (poisoning, shooting, trapping and culling) or non-lethal methods. Among the latter, the use of fertility control and particularly of an approach known as immunocontraception, is increasingly advocated to manage these conflicts. I also wish to emphasize that we do not consider contraception as the sole method to control populations of grey squirrel but we see this as one of the options in the tool box of methods to manage wildlife impact.
This is an illustration on how reproduction works : to prevent reproduction, we must target one of the several steps that lead to sperm production, ovulation and conception. One key hormone in this process, sometimes referred to as the "master hormone" is the GnRH (Gonadotropin Release Hormone) that initiates the cascade of reproductive processes.
Immunocontraceptives are vaccines that induce antibodies to proteins or hormones essential for reproduction. In particular, single-dose injectable vaccines are now available, targeting the GnRH, that render most animals infertile for several years, thus making practical applications credible. GnRH-based vaccines work by inducing antibodies that block the action of GnRH and, in turn, the production of sex hormones essential for reproduction.To be injected, animals must be captured first, which is labour intensive and thus expensive. Hence, the availability of oral immunocontraceptives would reduce significantly the cost and thus substantially broaden the scope of potential application of fertility control.
Work carried out by our group (funded by Defra) with our collaborators in the US showed that after a single injection of the vaccine most animals stop reproducing for several years.
An ideal oral contraceptive would have **no side effects** on welfare, physiology and behaviour, **long-term** effectiveness with single/few doses, be effective on/ deliverable only to **target species,** have no effects on **food chain** (predators,

risks to humans), be **inexpensive** to produce and administer and also be **deliverable to a large proportion of the population**

We have also modeled the population consequences of applying different levels of fertility control to grey squirrels. Our results sugges that a population (Y axis) is likely to be eradicated in a few years if > 70% of the animals is rendered infertile.

We know squirrel-specific hopper have been developed that can deliver bait to squirrel only, thus preventing non-target species from being affected by any drug.

So far, the advantages of GnRH vaccine-based contraception are that there are no persistent residues in treated animals, no known negative side-effects, GonaCon and another GmRH-based contraceptive (Improvac) are already registered in a few countries. The disadvantages are that an oral formulation is not yet available to induce immune response and we do not know how long the effect of an oral formulation will last. The National Wildlife Management Centre and our US collaborators tat the US Government's National Wildlife Research Center developed a small immunogenic molecule based on GnRH-based vaccine. **80% rats** fed this molecule had antibodies that suggested infertility. However, when this molecule was incorporated in a bait fewer rats responded and had lower antibodies to the vaccine. Hence a novel formulation is required for the oral vaccine to produces an increased immune response.

We have recently focused on oral contraceptives as the key way of realizing large-scale applications. Encapsulation technology is commonly employed in pharmaceutical preparations to achieve controlled drug release. Amongst novel technologies we identified the shells of spores and pollen grains as the most promising method to achieve our goal. Through this expanding technology, patented by the UK company Sporomex Limited, shells are emptied of their internal genetic material to obtain the sporopollenin exine capsules (SpECs) outer layer. SpECs have many advantageous properties for microencapsulation as detailed in this slide. In particular, this technology has been proven to have high bioadhesive properties that help maintain the capsules within an organism, and has been used successfully to increase the dlivery of fats, vitamins, enzymes, oils, hormones and other drugs such as ibuprofen.

More excitingly, a recent study showed that a model vaccine, delivered in SpECs and fed to mice, increased the serum and faecal antibodies in treated animals. The antibody response persisted for up to 7 months and the authors suggested that this was achieved as the spores embed themselves into the mouse gut wall. Crucially, this study offered a plausible mechanism for oral vaccination and demonstrated the potential to stimulate and to maintain the immune response for at least a few months.

The study we propose will identify the species of spores or pollen to encapsulate the novel contraceptive delivered to a model species (lab rat) in captive trials. These trials will be repeated with grey squirrels at our Animal Unit in York and followed by field pilot trials to confirm the efficacy of the contraceptive and to monitor the proportion of the population that will ingest the bait containing a placebo vaccine.Finally, we plan large-scale filed trials to monitor the effects of contraception at population level.

We believe this approach is scalable to a wide variety of species and diverse contexts. These include non-native invasive species, feral animals, overabundant wildlife, and contexts where culling is illegal, unfeasible or undesirable, where fertility control can complement culling to control populations or their economic and environmental impact.

In summary, we believe SEC-based oral immunocontraception has potential to revolutionise the mitigation of human-wildlife conflicts and that the approach is scalable to other species and contexts. So far, we have proven the effectiveness of injectable GnRH-based contraception, modelled the impact of fertility control on population dynamics. We also have candidate oral contraceptive and a delivery method available. We also have a proposal to confirm effectiveness of oral contraception and to test bait uptake by target proportions of grey squirrels and we are aware we must manage public expectations so that the public understands that we see contraception as complementary to other control methods. We need to conduct captive and field trials and to tackle the registration of drugs. To achieve this, funding, public support and stakeholder engagement will be crucial.

Thank you for listening. In case you need further information, please contact me at the e-mail shown on the slide. I am happy to take questions or to provide further details.

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