KEYNOTE: EPIZONE AND THE BTV-8 EPISODE, REMARKABLE TIMING AND OPPORTUNITIES!!

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In the 5-years of EPIZONE, many European countries have suffered from an outbreak of bluetongue virus serotype 8 (BTV-8). In this BTV-8 episode, research on bluetongue was significantly accelerated. Virological and serological diagnostics were developed and/or improved. Established assays were harmonised by efforts of EPIZONE and organized by the Community Reference Institute and others. New assays, like ELISAs for detection of BTV-antibodies in milk, and serotype-specific PCR-assays have reached the market and are thus commercially available. New assays to identify circulating viruses in more detail are under development. Several vectors, species of *Culicoides* and natural vector of BTV, were identified for transmission of BTV in the moderate climate of north-western Europe. On the other hand, the route of introduction of BTV-8 has been never discovered, and only little progress has been reported to unravel the mechanisms of the fast spread of BTV by these European tiny insects. Indeed young scientists with interest in entomology are educated, but the number of experienced entomologists is still very limited. A provisional vaccine for BTV-8 became available after two seasons of BTV-8, which has drastically reduced the number of infections. In general, this episode has also shown that awareness and preparedness should be improved. Collaboration and established networks like EPIZONE are tremendously important to combat diseases, in particularly vector-borne diseases, threating livestock and human health.

Southern European countries at the Mediterranean Basin are suffering from Bluetongue caused by several serotypes, 1, 2, 4, 8, 9, and 16, for more than 10 years. In August 2006, BTV-8, a serotype not previously circulating in Europe, was detected in north-western Europe. Most likely, the introduction had occurred a few months ago in Belgium, coincidently in the same time that EPIZONE was officially launched in Brussels. A few countries were affected by this BTV-serotype in 2006, but after a mild winter Bluetongue reappeared. Infections were reported at many places and in the same time, indicating that BTV-8 had easily 'overwintered'. A devastating season followed in which thousands of holdings became affected. The affected area expanded in all directions, including northwards and the overseas United Kingdom. Meanwhile, several companies started the development of an inactivated BTV-8 vaccine. After this devastating year, again a mild winter followed. In May 2008, provisionally inactivated vaccines were launched. Many countries promptly started voluntary or obligatory vaccination of ruminants. Reported cases dropped drastically in 2008, due to these vaccination campaigns, and likely by the high percentage of natural immunity in heavily affected areas. By testing for international trade purposes, surveillance, or increased alertness, the temporary presence of vaccine–related viruses and a new BTV-serotype were detected in this period. The next seasons were followed by much colder winters in N-W Europe. This likely decreased the chance on overwintering of BTV-8, but the enthusiasm of holders to vaccinate decreased. Anyway, after the first year of mass vaccination, it became remarkable 'quiet' and in some countries even completely 'silent'. In conclusion, the episode of BTV-8 has shown that unfortunate introduction of a vector-borne disease in N-W Europe could result in a huge outbreak with enormous impact on the economics and society. It seems to be that vaccination is the most effective measure to control this vector-borne disease.

Bluetongue is a disease in all ruminants caused by members of the BTV-serogroup within the genus *Orbivirus* of the family of *Reoviridae*. At least 24 BTV-serotypes have been recognized, and new serotypes are recently proposed, mainly based on genetic data. BTV-infections can run from completely subclinical to very severe resulting in death. This course is dependent on the isolate or strain, but is irrespective from the serotype. Virus transmission between ruminants, including cattle, sheep, and goats, occurs by bites of species of *Culicoides,* but only a few species (competent vectors) seems to be effective in transmission (spread). Several alternative routes of transmission have been described. These are not significant in endemic areas, but could play a role in transmission over long distances to BTV-free areas

(introduction), and/or after a long period without virus circulation (overwintering). Bluetongue is associated with the presence of competent vectors. Consequently, Bluetongue shows a seasonality and the affected area can vary dramatically over the years.

BTV-8 (IAH collection nr. BTV-8 NET2006/04) has caused a huge outbreak in N-W Europe, and is different from most strains so far. Fast spread by endemic *Culicoides* species in moderate climate conditions, more severe clinical signs in cattle, and transplacental transmission are a few examples. Orbivirological research has a long record; several excellent research groups have studied BTV and related orbiviruses for decades. Bluetongue virus (BTV) contains ten double stranded RNA segments encoding at least ten proteins. Seven are structural proteins, and can be found in the virus particle. Three of these, VP1, VP4 and VP6, contain enzymatic activities involved in replication and transcription of the BTV-genome segments. Structural proteins, VP3, VP7, VP2 and VP5, form the rigid virus particle. In addition, three nonstructural viral proteins, NS1, NS2, and NS3/3a cannot be detected in the virus particle, but are expressed in the cytoplasm of infected insect– or ruminant cells, and interact with the viral RNA and/or with cellular components.

In the recent five years, the 5-years of EPIZONE, and the BTV-8 episode, molecular orbivirology has made a breakthrough by the development of reverse genetics for BTV. This technology opens the way to generate all kind of reassortants and mutants of BTV. Unknown functions of viral proteins can be identified and will be studied in more detail. For the first time, functions of viral proteins as well as unique viral mechanisms and interactions with cellular proteins can be studied in the infected host or vector. Additionally, better and cost-effective vaccines could be developed to control outbreaks of Bluetongue. Expectedly, this breakthrough will also accelerate research on other orbiviruses of concern, like African horse sickness virus. At present, only a small step has made to explore the opportunities of this technology in orbivirus research. A few examples of results, like reassortants, serotyped virus, and mutations in structural and nonstructural proteins, are presented by posters. Here, some of the opportunities for future research on this intriguing vector-borne disease will be presented and discussed.