

Editorial

HCV, Dengue, West Nile and now Zika; What's next? The threat of endemic TBE relatives in Southern Europe

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The *Flaviviridae* threat

Flaviviridae is a family of viruses that infects vertebrates (Vlachakis *et al.* 2012). Virions of this family are enveloped and slightly pleomorphic during their life cycle. They are spherical in shape and usually 40-60 nm in diameter. Their nucleocapsids are isometric and sometimes penetrated by stain. The usual size of the nucleocapsids is 25-30 nm in diameter and they have a polyhedral symmetry (Vlachakis *et al.* 2013). *Flaviviridae* consist of three characterized genera and one unclassified genus (Loukatou *et al.* 2014). The *Flaviviridae* viral family includes a large number of highly pathogenic viruses. Both, farming and agriculture have suffered seriously in the past from the impact of *Flaviviridae* on livestock.

The Greek Goat Encephalitis (GGE) virus belongs to the genus Flavivirus, same as Zika. GGE virus, which is endemic in Greece is phylogenetically related to the Tick-borne encephalitis (TBE) viruses (Kochlios *et al.* 2012). TBE viruses are vector-specific, transmitted by the Ixodidae ticks (Figure 1). They have been recently suggested to belong to the same group with the louping ill virus. This group consists of four main subtypes: western TBE, eastern TBE, turkish sheep encephalitis and louping ill virus (Vlachakis *et al.* 2013).

This report aims to raise awareness against a probable outbreak of the currently latent GGE. Even though the virus is not currently in epidemic, we have numerous examples of animal diseases that due to neglect, got out of control with a devastating impact on both economy and society. GGE is a zoonotic disease that infects the central nervous system of livestock. Zoonotic diseases and infections are transmissible naturally from animals to humans and *vice-versa*. To date, more than 200 cases of zoonosis have been reported, some of which have had deplorable consequences in many societies around the world. Namely,

some of the most representative zoonotic diseases in epidemic either now or in recent history include: Anthrax, Bovine tuberculosis, Cholera, Cowpox, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathy (TSE), bovine spongiform encephalopathy (BSE) or "mad cow disease", Crimean-Congo hemorrhagic fever, Cutaneous larva migrans, Dengue fever, Ebola virus, Echinococcosis, H1N1 flu, Leishmaniasis, Mediterranean spotted fever, Rabies, Typhus, West Nile, Yellow fever and the recent Zika virus. It goes without saying, that any of the above diseases, besides from being major 'killers' have the potential to cripple even the most organized societies via impacts on public health, psychology, tourism, eating habits, commerce, import/export of goods and the overall quality of life.

GGE is an endemic Southern Europe variant of TBE

The Greek goat is one of the oldest and most domesticated species. It has been extensively used for its meat, milk and skins around the world since antiquity. Herein, we strive to alert and raise awareness against a probable outbreak of the Southern Europe endemic "ticking bomb" GGE virus, so that it may not end up in another form of tragedy. The first incident of GGE virus report in Greece was during the dengue epidemic outburst in 1927-1928. The next report took place in Vergina in 1969, where the prototype of the GGE virus was isolated from the brain of an encephalitis suffering newborn goat (Papadopoulos *et al.* 1971). Recent reports on the prevalence of GGE in Greece were conducted by hemagglutination inhibition tests. It was found that of all animals that live in northern Greece, 16.8% of goats, 5.6% of pigs, 5.1% of sheep, 4.7% of horses and 3.1% of cattle were positive to TBE antibodies (Pavlidou *et al.* 2007). Another most recent study (2003-2005) of animal screening in northern



Figure 1. Current geographical distribution of the *Ixode ricinus* and *Ixode persulcatus* species.

Greece, indicated that in the Chalkidiki prefecture 5.82% of all animal population bears antibodies to TBE based on seroepidemiologic tests (Papa *et al.* 2008).

Sheep and goat farming is predominantly a pasture-based activity, often found in the 'less-favoured areas' (LFAs) of the European Union (EU) (Papa *et al.* 2008). In some LFAs sheep and goat farming is the main source of economic activity and this has played a major role in shaping the landscape and the local environment. The three main goat producing member states are Greece (37.2%, 4.8 million heads), Spain (21.6%) and France (9.4%), and along with the United Kingdom account for nearly 80% of the EU sheepmeat/ goatmeat production. The EU is the second largest producer of sheepmeat and goatmeat in the world after China, where Greece's sheep and goat meat production was 104,760 tonnes in 2011 (Eurostat 2015). Of major concern are the control systems available to deal with disease outbreaks in the EU, although they only deal with particular diseases. Provided that members of the *Flaviviridae* family have reached epidemic dimensions in recent history in developed places of the world, it is of high importance to prevent a potential outbreak of the GGE virus, which would have major social and economic consequences in the Greek society. The examples of the Hepatitis C and Dengue viruses are quite alarming. More than 170 million people worldwide are currently chronically infected with the Hepatitis C virus. Hepatitis C has spread all over the world; notably, for every person who has the AIDS virus (HIV) four persons have the Hepatitis C Virus. In

the meantime, Dengue fever infects 50 million people per year in central Africa. According to WHO, all vector-borne diseases are expected to increase due to lack of effective agents and global warming (reviewed by Campbell-Lendrum *et al.* 2015).

It is remarkable that even though *Flaviviridae* are separated to different genera, they do not have common biological properties and do not show serological cross-reactivity. However, they manage to retain high similarity in the morphology of the virion, the organization of the viral genome, and the estimated life cycles and replication patterns that they follow. Based on our preliminary findings, there are 94 complete polyprotein sequences, the distribution of which in the 4 *Flaviviridae* genera is: Flavivirus (77), Hepacivirus (6), Pestivirus (7) and Unclassified Flaviviridae (7). Inhibition of the viral helicase is a very promising approach that is becoming increasingly popular. Helicases are capable of unwinding double stranded DNA and RNA to single strands by breaking the series of hydrogen bonds that keep the two strands together. The unwinding activity of the viral helicase is essential to the virus during its replication process. Mutated inactive helicases in Dengue and Bovine Diarrhea viruses led to reduced proliferation of the virus. It is believed that inhibition of the viral helicase will be an effective tool for the reduction of the replication rates of the *Flaviviridae* viruses. The viral Helicase is coded by the viral NS3B gene next to the NS3A gene, which codes for the viral Protease.

Conclusion

GGE is an endemic Southern European disease and, as such, not much aid is expected to come from the developed northern Europe or US. Innovative and original basic research needs to be conducted as a preventive measure to a latent virus, which, however, has the potential to blow out of proportion into a devastating threat for the Southern European economy and society. Despite the severity of the infections caused by almost all members of the *Flaviviridae* family, no specific antiviral therapy is available today. This renders the need for an anti-GGE virus drug design and GGE virus control strategy more urgent than ever, since the beleaguered Mediterranean societies would have a real hard time to cope with an epidemic infection both socially and financially.

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