poster 5.17

Arbovirus persistence in a seasonal environment

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Although transmitted by hematophagous insects which present a seasonal population dynamics and are almost inactive during the unfavourable period, vector-borne diseases may persist over several years in temperate climates with disastrous consequences for human and animal health (chikungunya, dengue fever, African horse sickness, etc ...). A better understanding of this persistence beyond the unfavorable season for vectors is a major scientific challenge to limit the emergence or reemergence of vector-borne diseases. In temperate climates and in the Sahel region, seasons regulate the life cycle of hematophagous insects. Hence, summer and the wet season are favorable to insects (and therefore to transmission), whereas winter and the dry season are unfavorable to insects that overwinter and therefore do no transmit pathogens anymore.

Three independent mechanisms enable a pathogen to persist beyond the unfavourable season for its vector: *i)* a low continuous transmission associated to the survival and a residual biting activity of the adult vector, *ii)* persistence in the host, and *iii)* persistence in the resistance stages of the vector. First, a continuous transmission could occur in regions where vectors bite hosts all year round, the low winter temperatures increasing the interval between two meals and the duration of the extrinsic incubation period. This mechanism could be involved in the virus persistence in the *Culex*/West Nile virus system in southern California. Moreover, pathogens may develop adaptive strategies against vector mechanisms to overpass unfavorable conditions. They may persist in the host or in vector resistance forms. Pathogen persistence in hosts can be related to a long viremia, to vertical transmission, or to a chronic infection phenomenon with resurgent viremia. For example, in the system *Culicoides*/bluetongue virus, cattle present a long viremia and the vertical transmission of the virus in the host is possible. In the system *Culex*/Western equine encephalitis virus, a resurgence of viremia has been observed experimentally in snakes after hibernation. Pathogen persistence in vector resistance form is possible only if there is vertical transmission, giving rise to infected eggs or newly emerged adults. For example, it is the case in the system mosquito/Japanese encephalitis virus.

The existence of each of these mechanisms has been demonstrated, experimentally and by field observations, for different biological host/vector/pathogen systems. In contrast, few studies have investigated several of these persistence mechanisms, illustrating the difficulty of quantifying the mechanism role under natural conditions. Little progress thus has been made to contradict Léon Rosen, who wrote in 1987: "at present, the mechanism by which mosquito-borne alphaviruses pass the winter is obscure". Actually, arbovirus persistence is an interesting model of a parasite developing adaptive mechanisms against the seasonal synchronization of host/vector pairs.

Using a modelling approach, we assessed the likelihood of mechanisms of arbovirus persistence beyond the unfavourable period for its vector according to the parameters driving these mechanisms and the host demographic regime. Modelling is a relevant approach for investigating a panel of persistence mechanisms highlighted in experimental and observational studies on one or another vector/pathogen system, and to compare the range of parameter values theoretically allowing persistence with the range of values determined experimentally. We studied the probability of virus persistence 5 years after its introduction in a naive host population, for all the persistence mechanisms identified. A compartmental stochastic model SIR/SEI (susceptible, infected, resistant for hosts; susceptible, exposed, infected for vectors) was used to assess persistence as the proportion of repetitions for which the virus was still pre-

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sent 5 years after introduction. A period of five years allows freeing from random persistence that may occur over a few years without a real link to the virus adaptation to a seasonal context. Moreover, on a longer term other factors than virus adaptation may favor persistence (change in vector availability, host susceptibility, etc). To consider a wide range of vector-borne diseases, three different host demographic regimes were considered. Initial model evaluations showed that without considering any of the persistence mechanisms the virus cannot persist even with extreme values of infection parameters.

The three mechanisms studied allow arbovirus persistence in a host population for given parameter values. Two types of threshold effects have been observed.

A first one leads to certain persistence for the highest parameter values and a demographic regime with a high turnover (as for birds). A second one leads to a decrease in persistence beyond a given value of parameters driving the mechanism, in relation with host demographic regime: if the turnover is too low (as for humans) to renew rapidly the susceptible population, persistence decreases.

Virus persistence in host during the unfavorable season appears to be an effective strategy to adapt to vector seasonal variations, either by a very long viremia in few individuals, or by vertical transmission. Reactivation of chronic infection seems rare for arboviruses, whereas it is classically described for parasites, as in the case of malaria. We propose a generic framework that can be adapted to any vector-borne disease as long as host and vector biology is known. This framework allows assessing the plausibility of each persistence mechanism in real epidemiological situations.