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Ocurrence of antiviral drug resistance mutations in A/H1N1pdm09 influenza virus neuraminidase gene in two consecutive seasonal epidemics

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Background: The study of the influenza viral genes using massive sequencing can lead to a better knowledge of the mutations related with resistance to flu antiviral drugs. A majority of patients that requires hospitalization due to flu infection have chronic underlying diseases, and those clinical conditions frequently prevent an efficient control of influenza virus infection. The immune dysfunction caused by flu viruses can lead the apparition of antiviral drug resistance mutations more frequently than in healthy people. The aim of this study is to describe and quantify the presence of antiviral drug

mutations in the neuraminidase (NA) gene of A/H1N1pdm09 flu virus in two different cohorts from two consecutive influenza seasonal epidemics.

Material/methods: We designed a prospective observational study recruiting 87 respiratory samples from hospitalized and ICU patients diagnosed for A/H1N1pdm09 influenza virus. These samples were obtained from several big hospitals of Spain (Valladolid, Barcelona and Madrid) during 2013-14 and 2014-15 influenza epidemics. The NA gene of influenza viruses isolated were deep sequenced using an Ion Torrent PGM platform (Applied Biosystems, Foster City, CA, USA) and PathAmp™ FluA reagents (Life Technologies, CA, USA). The sequences obtained were aligned using *Bioedit 7.2.3* software and mutations were analyzed according to the clinical features of patients with *FluSurver* free software.

Results: Globally we observed 6 different mutations related with resistance to antiviral drugs. The I117M mutation was the most frecuently observed in the viruses analyzed (n=48; 49.5%). This mutation was exclusively present in a subgroup of the viruses isolated during 2014-2015 influenza season. The remaining resistance mutations were obseved in low percentages (Y155F-1.0%; D199N-3.1%; S247N-1.0%;H275Y-1.0%) in viruses from both influenza seasons. We did not observe other described mutations related with resistance to antiviral drugs, such as V116K, I117V, E119D o R292K.

Conclusions: Our study show that flu viruses obtained from 2013-2014 and 2014-2015 influenza seasons in Spain had a modest number of different mutations related with resistance to antiviral drugs, but most of this mutations were concentrated in a very low percentage of the viruses analyzed. This phenomenon has been observed recently in others works. However, in the present study we characterized the presence of a large cluster of influenza A/H1N1pdm09 viruses harboring the I117M mutation which contributes to a moderate Oseltamivir resistance whether in presence or absence of H275Y mutations.