

Understanding the selection process of adaptive mutations 271A, 590S and 591R in the PB2 polymerase during the emergence of the triple-reassortant H3N2 swine influenza virus

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In 1998, an H3N2 swine influenza virus emerged following reassortment between avian, human, and swine viruses, acquiring avian-derived PB2 and PA segments. PB2 subsequently adapted to pigs through the acquisition of the triple mutation 271A, 590S, and 591R. Although the key role of the viral polymerase complex in the adaptation of avian influenza A viruses to mammals is well established, and these three mutations were conserved in H1N1pdm09, the contribution of this combination of mutations and the context in which it was selected remain poorly understood. Using a loss-of-function approach, we compared the replication of four variants of the 1998 H3N2 triple-reassortant swine virus carrying different combinations of avian- and swine-derived PB2 and PA segments *in vitro* in MDCK and NPTr cells and *ex vivo* in swine precision-cut lung slices (PCLS), using replication kinetics and serial passage experiments. We found that PB2 mutations 271A, 590S, and 591R conferred only a moderate selective advantage when associated with a swine-derived PA, but a markedly greater advantage in the presence of an avian-derived PA. Our study highlights the importance of the viral genetic background in shaping the phenotypic effects of adaptive mutations and emphasizes the need to consider interactions between viral genes when assessing influenza emergence and pandemic risk. These findings suggest that the PB2 triple mutation may have been selected in swine before PA adapted to its new host.

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adaptative mutations, interactions, selection, emergence

Professional status of the speaker

PhD student

Junior scientist status

Yes, I am a junior scientist.

Registration ID

INF26-61

Author: SARRAT, Margot (INRAE ENVT)

Co-authors: Ms MOMPART, Florence (INRAE ENVT); Mr PEYRET, Thomas (INRAE ENVT); Ms SIKT, Fatima (INRAE ENVT); Ms NAZNIN, Baby (INRAE ENVT); Ms CAMUS, Christelle (INRAE ENVT); Mr VOLMER, Romain (INRAE ENVT)

Presenter: SARRAT, Margot (INRAE ENVT)

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