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Panorama

Influenza outbreak, a year after the pandemic, what have we learned?

Brote de influenza, un año después de la pandemia, ¿qué hemos aprendido?

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The first conference on zoonoses and emerging diseases was held in Barcelona last June, in the facilities of Cosmocaixa foundation. The conference was organized by the Centre for Research in the Animal Health (CRESA) and the Spanish Society for Virology, and other collaborative societies such as the Spanish Society for Immunology (SEI).

This first conference was presented under the heading "Avian and Swine flu: current status and future prospects" and the speakers offered a review of the various issues surrounding the flu virus, considering the strains that affect humans and poultry and pork, from a strictly scientific point of view. Among others, addressed issues included basic science, health surveillance and epidemiology.

The conference featured a brief but interesting opening by Dr. Mariano Domingo, director of CRESA, who introduced the four greatest (flu) threats that the scientific community is facing. According to Professor Domingo, these four threats respond to the letters H7N1, H1N1 classical, H1N1 pandemic (pH1N1) and H5N1. Each of these viruses wears a "shell" distinctively represented by the specificity of hemagglutinin (H) and neuraminidase (N), providing them with their characteristic biology and pathology. Thus, it is considered that the most virulent strains of influenza viruses are characterized by expressing H5 and H7, without underestimating the infectious capacity of the other pathological strains. These strains are subjected to a continuous surveillance in the veterinary environment and poultry production, as Concepción

Gómez-Tejedor, General Coordinator of the Dirección General de Recursos Agrícolas y Ganaderos del Ministerio de Medio Ambiente, Medio Rural y Marino, stated in her presentation. The results on the dynamics of infection by influenza virus in birds and the epidemiology of avian and swine presented by Dr. Natàlia Majó and Dr. Jordi Casal (CRESA, Barcelona) confirmed those data. Monitoring and control data about influenza in the national health system were presented by Dr. Pilar Pérez (ISCIII, Madrid) based in the network of specialized laboratories (RELEG). This network relies on a series of sentinel laboratories in each region, a national reference laboratory (ISCIII) and three national centers of the WHO. This network permitted a detailed monitoring of the pandemic flu and its evolution in Spain, as well as a detailed study of the strains isolated from patients and their resistance to some drugs (oseltamivir).

Of the threats mentioned above, perhaps the most striking is the pH1N1 because of the pandemic outbreak at the end of last year. Currently, pH1N1 is considered a "seasonal" virus, although experts believe we should perhaps look more closely to this virus.

The major impact of pH1N1 on the media has managed to eclipse H5N1, which caused great concern in 2003 because of the massive affection in domestic poultry in the Far East and the high mortality rates in infected humans. However, the experts believe that this is much more dangerous than pH1N1, and should be closely monitored. Today H5N1 is still detected sporadically in parts of Indonesia and Southeast Asia.

Influenza virus and immune system

The pandemic human influenza viruses are characterized by the presence of a new hemagglutinin (H) that allows them to evade pre-existing immunity against previous viruses. These changes in H occur by two mechanisms known as “antigenic drift” (minor changes) and “antigenic shift” (major changes). In the first case, the changes involve certain nucleotides that are located in the antigenic zones of the H. In the latter case, the recombination that may occur between different species or quasispecies of viruses generates the emergence of new viruses with different H molecules. Such hemagglutinins emerge from strains of virus adapted to animal hosts where, in many cases, infection progresses asymptotically. However, despite the origin of the H and perhaps other viral genes from non-human flu, a pandemic virus needs to be transmitted among humans and, therefore, adapted to infect, replicate and transmit in humans. The H1N1 virus of 2009, despite being genetically similar to swine flu virus and despite a pre-existing immunity against H1N1 viruses in humans, was able to start a pandemic outbreak.

The pH1N1 virus is considered to be the product of recombinant pig H1N1 virus, avian H1N1 and human H3N2 viruses (fig. 1). Studies in the laboratory of Dr. García-Sastre (Mount Sinai School of Medicine, New York) identified the pH1N1 M gene responsible for its transmissibility in humans but not to other species. However, in spite of the social alarm caused, the pH1N1 has not proved as virulent as the famous 1918 H1N1 strain that caused the so-called Spanish

flu. However pH1N1 contains an interesting relationship with this historic of the virology. Up-to-date epidemiological studies show a significant increase in the frequency of infection among younger individuals. Furthermore, the presence of neutralizing antibodies in the sera of individuals older than 45-50 years seems to indicate a prior immunization in these subjects, but not in younger individuals. There have been several waves of H1N1 virus, from the famous 1918 influenza epidemic to 1957 and most recently in the 70's. However, infection rates in individuals under 40 years were higher than in older individuals. According to García-Sastre, the explanation lies in an “antigenic drift” affecting the epitope SA of the H in the 1970 virus compared to the 1918 virus. Thus, being the virus pH1N1 2009 more similar to the 1918-1957 viruses, these individuals would be partially protected by neutralizing antibodies against a similar H, while the lower antigenic shift suffered by the 1970 strain does not allow such antibodies to recognize the 2009 strain H protein. Thus, antigenwise, subjects born after 1970 would suffer a “primary infection” by pH1N1, which could partly explain the observed epidemiological phenomena.

Until the advent of pH1N1, swine influenza virus (SIV) has merited less attention compared with the increasing knowledge about influenza viruses that affect human or poultry. Dr. Maria Montoya's lab (CReSA, Barcelona) presented results showing profound changes in the swine immune system following an interaction with the SIV H3N2. Data presented by Dr. Jordi Casal (CReSA, Barcelona) confirmed that farms in Spain have a high prevalence of SIV types H1N1, H3N2, and H1N2. Therefore, following the appearance of pH1N1 last year, the

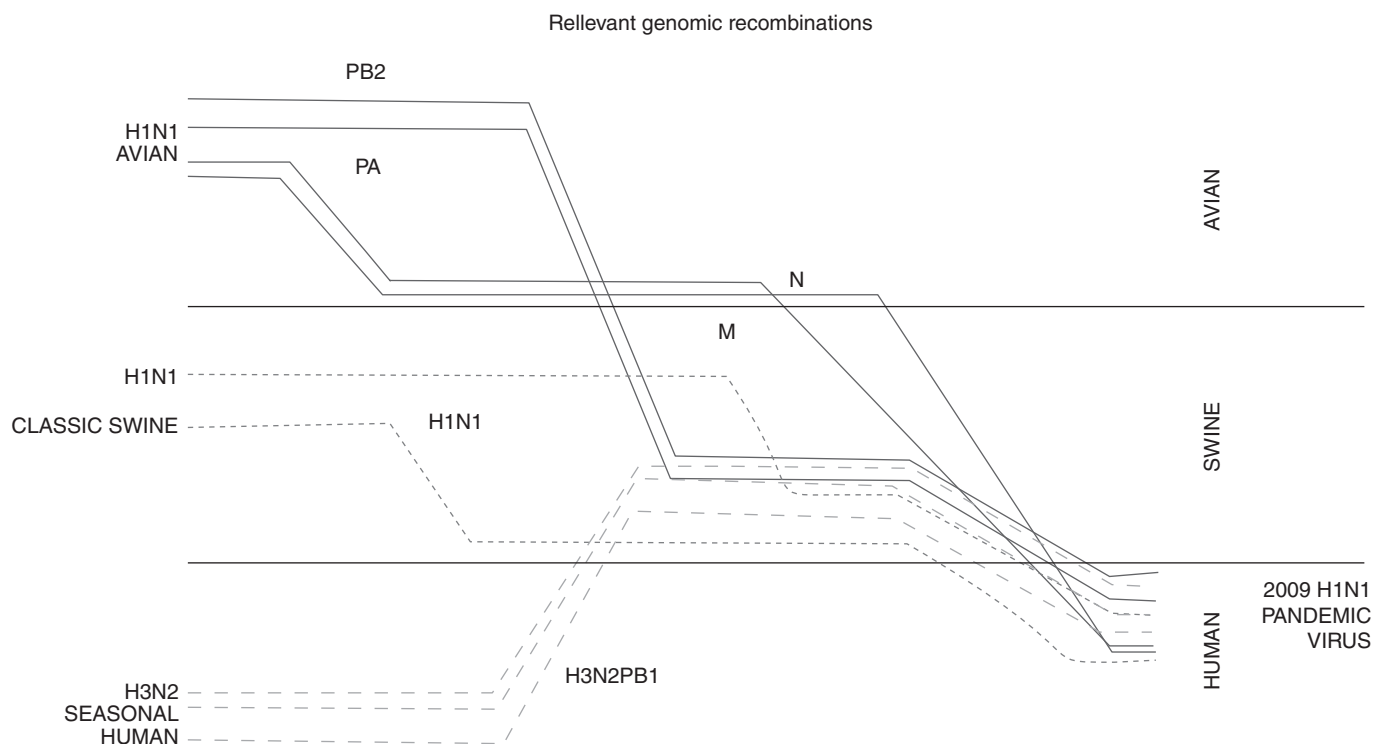


Figure 1 - Putative genetic recombinations that have allegedly led to the emergence of the pH1N1 virus (adapted from Smith et al. Nature. 2009).

group of Dr. Montoya questioned whether the existence of a prior infection with H1N1 circulating SIV conferred some cross protection against infection with pH1N1. The results obtained showed the existence of cross-protection where humoral immunity appears to play a crucial role.

Moreover, influenza viruses are endowed with special features, as explained by Dr. Amelia Nieto (CNB, Madrid). Specifically, influenza virus uses a rare transcription strategy. The viral polymerase binds to the cap structure of cellular mRNAs synthesized *de novo* and produces an endonucleolytic cut about 12-13 nucleotides far from this structure. These cap-oligonucleotides are then used as primers for the synthesis of viral mRNAs. The interaction of viral polymerase and cellular RNA polymerase II, and that of viral polymerase with other cellular proteins and factors related to transcription have been described. Finally, the polymerase itself induces a degradative process of cell specific transcription factors once the viral transcription has been completed and the link is no longer necessary. The data presented by Dr. Nieto suggest that during infection, influenza viruses manipulate the cellular transcription machinery contributing to the inhibition of the antiviral response of the host cell and to viral pathogenicity. Interestingly, these processes are carried out by pathogenic strains but not attenuated virus strains.

Consequences of the pandemic. Vaccination

Dr. Tomas Pumarola (UB, Barcelona) explained the strategy of the Department of Health of the Generalitat of Catalonia against the pandemic and presented epidemiological findings of pandemic influenza in Catalonia. Dr. Pumarola stated that these data were similar to those obtained in Spain, and therefore could be extrapolated.

Following the first phase of containment of the pandemic flu, a second phase of mitigation was launched in July 2009, when 224 cases of influenza pH1N1 were detected. In September of that year, with data obtained from the southern hemisphere (mainly from Australia and New Zealand), experts began to consider pH1N1 as "seasonal" flu. Epidemiological data showed that the majority of affected individuals were under 40 years of age, 50% of them suffering of a primary viral pneumonia with no previous risk factor in a 32% of the cases.

Epidemiological data in Catalonia showed 2000 affected/100 000 inhabitants between the ages of 0 to 14 with a 17% of deaths. The age range between 15 to 65 showed 200 cases/150 000 inhabitants with a mortality rate of 20%, while among adults over 65 there were a few cases but most of them were serious. These data could suggest a possible protective factor, corroborating the results reported previously by García-Sastre.

Regarding preventive vaccination, only 19% of the target population received the vaccine. This can be explained in part by the low perceived risk of infection detected in the general population (according to an official survey). However, other factors involving media were not discarded, such as unconfidence on the pharmaceutical industry and the confusing contribution of some health professionals and graduates that appeared in the media. In this sense, the need to clearly explain the benefits of vaccination to the general population was stressed. More specifically, the need to raise health professionals' awareness of this issue because they are in direct contact with the patient and convey their views directly. Later, the roundtable stated the general consensus that one of the areas in which the scientific community can help society —eventually if a new pandemic outbreak takes place— is through scientific societies. It was proposed that the relevant scientific societies publish joint press releases to explain the details of possible future outbreaks.

The presence of science communication professionals was a positive point in this journey. Dr. Alvaro Arjona (Thomson Reuters Health & Science) made a presentation of the general methods of handling, processing and consolidating scientific information for the dissemination of biomedical progress and development of therapies. The final panel of the conference discussed the need for a greater collaboration between media and the scientific community, with particular emphasis on the role played by professional scientific societies as a bridge between scientists and health professionals, press and society in general to avoid unnecessary panic and misunderstanding.

Finally, we believe that it is important to emphasize the benefits that multidisciplinary forums should have (basic science, epidemiology, health surveillance, press) in addressing complex issues such as influenza virus (human, avian, swine) and think that they should be encouraged in the future.