

Weakened immunity in aged hosts with comorbidities as a risk factor for the emergence of influenza A H7N9 mutants

Jesus F. Bermejo-Martin^{1,2}, Raquel Almansa^{1,2}, Raul Ortiz de Lejarazu^{1,2}

¹Hospital Clínico Universitario de Valladolid, (SACYL & IECSCYL), Avda Ramón y Cajal, Valladolid, 47005, National Health System, Spain

²Nacional Influenza Center, University of Valladolid, Avda Ramón y Cajal, Valladolid, 47005, Spain

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Following a recent report, the median age for patients with confirmed H7N9 virus infection is 61 years old with 42.3% of patients being 65 years of age or older [1]. A total of 61.3% of the patients had at least one underlying medical condition. H7N9 infection causes severe illness, including pneumonia and ARDS [2]. A recent epidemiological survey seeking influenza-like illness caused by avian influenza A[H7N9] confirms the preferential targeting of the elderly by this virus, since it found no evidence of widespread mild disease in young people in the Chinese provinces with confirmed human cases of infection [3]. The virus preferentially targets elderly people with comorbidities due probably to the weak immune status of this demographic. Ageing is associated with a decline in the diversity of the T cell's repertoire, leading to impaired immunity to influenza [4]. In turn, the presence of comorbidities such as diabetes, chronic obstructive pulmonary disease, or hepatitis B co-infection could impair host response to infection [5]. In fact, the higher incidence of influenza A/H7N9 infection in males (68.5%) could be due to the higher frequency of comorbidities generally observed in men [1].

As described by Nuño *et al.* [6], weak immunity can facilitate the survival of less fit influenza strains and the generation of novel influenza strains by increasing genotype diversity [6]. In this regard, during the [H1N1] pandemic of 2009, immunosuppression was associated with the emergence of oseltamivir-resistant strains [7]. A recent communication by Hu Y *et al.* in *Lancet* reports the emergence of neuraminidase Arg292Lys mutation in

two patients who also received corticosteroid treatment [8]. This mutation is known to confer resistance to both zanamivir and oseltamivir. Furthermore, in individuals with prolonged infection, failure to limit the infection to the upper airway is a proposed mechanism for the emergence of viral genomes with the haemagglutinin mutation D222G (a determinant of virulence) [9].

Studies on a ferret model conducted by an international team have demonstrated that under appropriate conditions, human-to-human transmission of the H7N9 virus may be possible [10]. As mentioned above, the immunological status of the elderly host with accompanying co-morbidities could increase the risk of infection. In patients with weak immunity, viral clearance is delayed, and viral shedding is prolonged. If the virus fully adapts to humans, the appearance of viral “super-spreaders” could result.

Consequently, the preferential infection of patients with potential immunosuppressive conditions such as ageing or the presence of concomitant comorbidities constitutes an additional cause of concern in the current outbreak of influenza A/H7N9, since it could contribute to the emergence of new mutant strains, with important potential consequences on viral adaptation to humans and resistance to antivirals. In this context, early treatment of the infected patients with neuraminidase inhibitors could play a major role in preventing the generation of new mutants [11]. Evaluating the immune status of patients with severe respiratory disease caused by H7N9 could lead to important clues to designing better treatment strategies [12].

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Corresponding author

Jesus F Bermejo-Martin JF
 Unidad de Investigación Biomédica
 Hospital Clínico Universitario de Valladolid
 (SACYL & IECSCYL)
 National Health System, Spain
 Avda Ramón y Cajal
 Valladolid, 47005
 Spain
 Telephone/Fax:
 Email: jfbermejo@saludcastillayleon.es

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