Letter to the editor. Virological analysis of fatal influenza cases in the United Kingdom during the early wave of influenza in winter 2010/11

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To the editor: In response to the paper by Ellis *et al.* [1], published in *Eurosurveillance* Volume 16, issue 1, we would like to make a few observations.

D222G/N substitutions in the haemagglutinin of influenza A(H1N1)2009 strains have been associated with increased virulence [2-4].

An enhanced binding affinity of the mutated haemagglutinin to the α -2,3 sialic acid receptor rather than to the α -2,6 sialic acid receptor has been postulated to be the basis of the increased virulence of D222G/N mutants [3]. The α -2,3 sialic acid receptor is present at higher density on the surface of the cells of the lower respiratory tract tissues whereas the α -2,6 sialic acid receptor is present at higher density on the surface of cells of the upper respiratory tract tissues.

In surveillance reports from different countries, the overall presence of such mutants ranged from 2.0% to 5.6%, while it was significantly higher (up to 22.9%) in severe or in fatal cases [2-4]. Interestingly, the paper by Kilander *et al.*, analysing both nasal swabs and bronchoalveolar lavage, showed the highest rate of D222G/N mutants in patients with severe and fatal infections [2]. In a multicenter study, we analysed paired nasal swabs and bronchoalveolar lavage samples from patients admitted to intensive care units for mechanical ventilation or extracorporeal membrane oxygenation. The samples were compared with samples from patients with pneumonia not requiring mechanical ventilation and from community patients. Our data showed that D222G/N mutants were more frequently detected in lower respiratory tract secretions than in secretions from the higher respiratory tract [5]. In addition, by combining data from nasal swabs and bronchoalveolar lavage samples, the frequency of D222G/N mutants in patients with severe infections increased to 43.0%, as compared to 7.8% and 0% in patients with moderate and mild infections, respectively [5]. In agreement with the pathogenetic hypothesis considering the lower respiratory tract as the more favorable environment

for replication of such mutants, viral RNA levels were significantly higher in bronchoalveolar lavage samples than in nasal swabs [5].

Ellis *et al.* reported that almost all viruses derived from fatal and non-fatal cases analysed (39/41) in the United Kingdom during the early wave of the 2010/11 influenza winter season showed the wild-type 222D haemagglutinin residue [1]. Thus, in the paper by Ellis *et al.*, severe and fatal influenza cases were not associated with the emergence of D222G/N mutants, even though the role of other aminoacid substitutions remains to be determined [1]. The authors of this study do not specify the type of clinical samples used for analysis. In the case they used nasal swabs only, on the basis of the above-referenced studies, the rate of D222G/N mutants might have been underestimated.

For a better understanding of the mechanisms of influenza A pathogenicity and the epidemiology of severe and fatal events, the analysis of bronchoalveolar lavage specimens in parallel with nasal swab specimens from patients admitted to intensive care units for severe infections should be envisaged. Additionally, a post-mortem analysis of tissues and/or secretions from the lower respiratory tract from deceased patients, in the event they had not been previously analysed, is important.

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