Authors’ reply. Virological analysis of fatal influenza cases in the United Kingdom during the early wave of influenza in winter 2010/11

J Ellis (joanna.ellis@hpa.org.uk), M Galiano, R Pebody, A Lackenby, CI Thompson, A Bermingham, E McLean, H Zhao, S Bolotin, O Dar, J M Watson, M Zambon
1. Health Protection Agency, Centre for Infections, London, United Kingdom


To the editors: Our Italian colleagues provide commentary on an important question, as yet unresolved, regarding the relationship between pathogenesis of influenza A(H1N1)2009 infection and mutation in particular viral genes contributing to virulence. Viral haemagglutinin (HA) is the key virulence determining gene for influenza in birds, and a major determinant for host cell tropism in mammalian influenza [1]. The link between cell tropism and virulence in humans remains unclear; many different approaches to this question conclude that virulence is associated with multiple viral genes, including genes determining replication efficiency (polymerase genes) and non-structural genes governing the interaction with the host immune response.

The emergence of animal viruses into the human population is associated with adaptive mutations [2-3] and tracking substitutions at residues known to be associated with such adaptive changes is an important surveillance function. The commentary highlights the opportunities arising from surveillance to develop and apply hypothesis generating questions from observational data sets.

During the 2009 pandemic, attention has focussed on amino acid substitutions at position 222 in the HA of influenza A(H5N1)2009 viruses, which has been observed to vary [4], with aspartic acid (D), glutamic acid (E), asparagine (N) and glycine (G) residues being present at this position. There is a clear correlation between enhanced binding to α2-3-linked sialyl receptor sequences by 222G variants and increased infection of ciliated epithelial cells in vitro models [5].

Our rapid communication of data obtained during the early phase of the epidemic in winter 2010 in the United Kingdom, using available material predominantly derived from swabs taken at the point of diagnosis from the upper respiratory tract (URT), was intended to provide a comprehensive update from all available sources, to give as full a picture as possible. We agree that wherever possible, when URT and lower respiratory tract (LRT) samples are available from individual cases, analysis in parallel is important, as well as sequential sampling from individuals who are hospitalised with severe illness. The ability to link both of these observations to clinical outcome and “within host” variation or evolution is important. We recognise that there is an inherent bias in such an approach, as individuals in the community are almost never sampled from the LRT, leading to the possibility of over interpretation of the importance of a single mutation, by focussing only on severe cases, but analysis of clinical outcome and its relationship to whole genome genetic composition of influenza viruses is underway in several different centres internationally.

The selection and emergence of the D222G mutation as a cause or consequence of more severe lower respiratory tract infection is still to be resolved. Emergence of this mutant is likely to exacerbate severity of disease, but by itself, may be neither necessary nor sufficient to account for a severe disease outcome, which is invariably a balance between virus virulence factors and host immune response capability. Further work is needed, both at the level of reductionist experimental pathology work in the animal model, and at the observational level in human populations. Detailed studies such as the Mechanisms of Severe Acute Influenza Consortium (MOSAIC) study [6], which focus on analysis of viral virulence and host immune response in severe illness, are likely to provide insights useful to understanding pathogenesis in humans. We thank our colleagues for raising this comment and for the opportunity to broaden the commentary in more detail than was possible in the original article.

References


