

Preliminary review of D222G amino acid substitution in the haemagglutinin of pandemic influenza A (H1N1) 2009 viruses

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Summary

Since the first appearance of pandemic influenza A (H1N1) 2009 viruses, certain mutations including those leading to the D222G substitution in the haemagglutinin (HA) protein and the K340N substitution in the polymerase basic protein 2 (PB2) have appeared sporadically. These substitutions in HA and/or PB2 have been reported in viruses obtained from mild to severe to fatal illness case but such viruses have neither formed distinct phylogenetic clusterings nor been associated with consistent changes in virus antigenicity. Based on currently available virological, epidemiological, and clinical information, the D222G substitution does not appear to pose a major public health issue. However, the World Health Organization's (WHO) Global Influenza Surveillance Network (GISN) and its partners will continue to closely monitor pandemic viruses for the D222G and other amino acid substitutions and continually assess associated risks.

Background

Influenza viruses are known for their high evolutionary rate and tendency to acquire point mutations at different positions in their genomes. Some mutations can result in amino acid substitutions at key locations in proteins, such as antigenic sites or the receptor binding site of the HA, and can alter properties such as those associated with the virus antigenicity or pathogenicity. Recently, the D222G substitution was observed in the HA of pandemic (H1N1) 2009 viruses isolated from fatal cases in several countries. The WHO organized a global teleconference with experts from GISN laboratories, external research institutions, and WHO Regional Offices to assess the public health significance. This review is based on those data and other information provided by GISN laboratories.

Detection of D222G substitution by GISN

The D222G substitution has been detected in virus isolates from around 20 countries, areas, and territories in the Americas, Asia, Europe, and Oceania. These changes have been found since April 2009 but not been associated with temporal or geographical clustering, strongly suggesting the mutation in these viruses have occurred sporadically as opposed to the emergence and sustained transmission of a variant virus. Based on

currently available data shared with WHO, the prevalence of D222G substitution is less than 1.8% (52 detections among more than 2755 HA sequences). Of 364 fatal cases analysed to date, viruses from 26 cases (7.1%) had the D222G substitution. The clinical information about potential underlying medical conditions in these cases is limited. Surveillance and laboratory analysis efforts to study this substitution have given priority to specimens from hospitalized and severely ill patients, leading to potential biases in the data. Additionally, a study done by the WHO Collaborating Centres for Reference and Research on Influenza (WHOCC) in Atlanta located in the Centers for Disease Control and Prevention (CDC) found the D222G substitution in 14 virus isolates but not in viruses in the original clinical specimens indicating the D222G substitution in these 14 virus isolates occurred after growth in the laboratory. These observations have made determining the clinical relevance of this substitution difficult.

Otherwise, the pandemic (H1N1) 2009 viruses with D222G substitution have been antigenically similar to the A/California/7/2009 (H1N1) virus, the WHO-recommended vaccine virus. Three of the D222G variant viruses carry the H275Y substitution in the neuraminidase (NA) associated with oseltamivir resistance.

Other substitutions of potential public health significance

WHO has been monitoring several other reported substitutions in the HA (D222E and D222N) and K340N substitution in PB2. The clinical significance of these substitutions remains uncertain.

Ongoing Studies

Preliminary results from in-vitro studies suggest that D222G substitution in the HA might increase binding to α 2-3 sialic acid (avian-like) cell receptors. Ferret studies have shown that viruses with D222G substitution, whose virulence is similar to wild-type viruses lacking this mutation, can be transmitted efficiently. Studies using mice and guinea pigs are ongoing to better characterize the receptor binding specificity, replication fitness, transmissibility and pathogenicity of viruses with this D222G substitution alone or in combination with other substitutions.

More detailed information on clinical, epidemiological and viral features are needed to assess the future public health significance of these viruses.