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OPINIONS AND PERSPECTIVE

Influenza Virus Co-Circulation and Emergence of New Variants.

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OPINION AND PERSPECTIVE:

The "Spanish flu" caused by 1918 Influenza A H1N1 virus was the first recorded devastating Influenza pandemic which took the lives of millions of people. It's almost a decade ago, after reconstructing and characterizing the genes responsible for its extra-ordinary virulence and transmissibility; still it is the virus which is continuously evolving, re-emerging and learning more and more about how to evade host immune response as well as to resist the anti-viral agents and be successful. But unfortunately we fail at identifying the solutions for the mystery of Influenza virus evolution. A writer, Richard Reeves has quoted about Influenza as follows- "It is perfectly obvious that no one or any single country can save the world from the horrors of tsunamis, hurricanes, earthquakes and winged influenza".

So this is one of the greatest challenges the scientific world is facing and we should continue our search till we attain the solution. After the 1918 H1N1 pandemic, descendants of the 1918 H1N1 strain as well as other subtypes of Influenza virus have emerged and re-emerged and circulated in the human population causing mild epidemics and devastating pandemics. Usually the pattern is such that the pre-existing strains being replaced by a novel strain which may cause the next pandemic. It was also earlier believed that co-circulation of Influenza subtypes did not occur but this is not the case with H3N2 strain which continues circulating since 1977 with the H1N1 strain till date. This phenomenon in which Influenza A H3N2 & H1N1 subtypes co-circulate is poorly understood. Significance of such a co-existence is that if two antigenically similar strains of the same subtype co-circulate in the human population, the genetic diversity of the circulating virus increases through mutations and re-assortments resulting in antigenically novel strains. It is believed that the co-circulating minor clade may provide haemmagglutinin gene that later became part of the dominant strain. Not only that, the outcome of the infection is dependent on whether the host had prior exposure to a related strain. And if so, there is a high chance that a highly pathogenic strain may get mutated. On the other contrary, it is also observed that inter-subtype re-assortment between Influenza A H1N1 and H3N2 viruses is not observed so frequently, despite its co-circulation. Therefore more studies needs to be conducted to throw light on the aspects of co-circulation whether the minor clade is complementing the existence and lethality of the major clade to help it to evolve into an antigenically novel strain or a minor unrecognized strain. In this regard, a comparative genomic analysis and characterization of both the strains in the same setting and exploring the interactions among them is crucial in unraveling new insights about the mysteries of Influenza virus evolution.

The significance of co-circulation of A/H3N2 and A/H1N1 dates back to 1977 when the Russian' influenza was caused by influenza viruses of the H1N1 subtype that closely resembled viruses that had circulated in the early 1950s. The re-emerging H1N1 virus did not replace the 1968 H3N2 viruses circulating at the time, and both subtypes are co-circulating in humans to this day. Re-assortment between viruses of these subtypes resulted in the emergence of H1N2 viruses in human populations in 2001 (Neumann G, 2009). Most influenza seasons were characterized by a co-circulation of at least two different lineages of H3N2 viruses.

Genetic re-assortment between H3N2 viruses belonging to separate lineages caused the different evolutionary pathways of the HA (Schweiger B., 2006). Morens et. al in 2010 also described that H3N2 influenza viruses have been co-circulating with the 1918 H1N1 virus descendants for about nearly three decades and is continued up till today. Nelson M I et al in 2007 extensively studied about the co-circulation of A/ H3N2 and A/ H1N1 strains in his study on molecular epidemiology of A/H3N2 and A/H1N1 Influenza virus during a single epidemic season in the United States, he observed that co-circulating clades of the same subtype exchanged genome segments through re-assortment, producing both a minor clade of A/H3N2 viruses that appears to have re-acquired sensitivity to the adamantine class of antiviral drugs, as well as a likely antigenically distinct A/H1N1 clade that became globally dominant following this season (Martha I.N 2008). He stated that there is still considerable debate over what

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aspects of influenza epidemiology so strongly favor the survival of a single HA1 trunk lineage in human A/H3N2 viruses, whereas multiple lineages seem to co-circulate more frequently within populations of human H1N1 (Martha I.N 2007). Alice et. al in 2009 has explained about the generation of genetic diversity and antigenic drift when two antigenically similar subtypes of Influenza virus co-circulate in humans producing re-assortants. As these viruses continue to circulate, immunity against them builds up in the host population. In parallel, viruses with mutations affecting the antigenic regions of the surface proteins accumulate in the viral population. At some point a novel antigenic drift variant, which is less affected by immunity in the human population, is generated. This variant is able to cause widespread infection and founds a new cluster of antigenically similar strains (Alice., 2009). On the other hand the limited genetic diversity among the co-circulating strains was explained by Andrew et.al in 2008. He studied the genomic and epidemiological dynamics of Influenza virus suggests that strong natural selection reduces the level of diversity that co-circulates at any given time. Cox et. al. in 2000 has also observed that each successive antigenic variant replaces its predecessor such that the co-circulation of distinct antigenic variants of a given subtype either did not occur or occurs for relatively short periods. Nelson et. al. also addressed the issue on both sides. He tries to explain why inter-subtype re-assortment between A/H1N1 and A/H3N2 viruses is not observed more commonly, despite the apparent co-circulation of both subtypes over both time and space. It is possible that a virus produced by inter-subtype re-assortment has a lower fitness, because the greater genetic distance between the A/H1N1 and A/H3N2 subtypes means that re-assortment events are more likely to disrupt essential functional interactions among segments. Even though researchers have attempted to address this contradictory issue, the genome-scale evolutionary dynamics of this phenomenon in which the A/H3N2 and A/H1N1 subtypes co-circulate, is still poorly understood. At national level, there are no reports on studies of molecular epidemiology of Influenza or its characterization. Not much original work has been reported from any other parts of the world regarding the effects of co-circulation of Influenza subtypes. Much of the articles cited here included reviews. At this perspective, it is clear that the attempt to study the evolution of Influenza virus in terms of its co-circulation with other subtypes gain much significance.

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