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P1-115 SCHOLARSHIP Promising Investigator Scholarship

Novel avian-origin influenza A (H7N9) virus attaches to epithelium in both upper and lower respiratory tract of humans

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Background: In March 2013, an avian origin H7N9 virus emerged in China, causing severe pneumonia and acute respiratory distress syndrome in humans, with limited human-to-human transmission. Some of the human isolates contained a Q226L mutation in the HA, which is known to be associated with a switch in the receptor binding preference of HA from alpha-2,3-linked sialic acids to alpha-2,6- linked sialic acids. The receptor preference of influenza viruses is an important factor in the cell tropism. Previously, we studied the cell tropism of influenza viruses by attachment studies, which showed that the pattern of attachment is associated to both the pathogenesis and transmission efficiency. Viruses that transmit efficiently among humans (seasonal influenza viruses) attach abundantly to epithelial cells of the upper respiratory tract. Furthermore, viruses which cause a severe pneumonia (HPAI H5N1) attach to type II pneumocytes and alveolar macrophages in the alveoli. Therefore, the goal of this study was to determine the attachment pattern of A/Shanghai/1/13 or A/Anhui/1/13, the latter containing the Q226L mutation throughout the human respiratory tract. Materials and Methods: Human tissues from the nasal concha, trachea, bronchus, bronchiole, and alveoli were included to determine the attachment pattern of reassortant viruses consisting of seven gene segments of influenza virus A/PR/8/34 and the HA of either influenza virus A/Shanghai/1/13 or A/Anhui/1/13 using virus histochemistry. In addition, we determined the attachment pattern in the respiratory tract ferrets, mammals that are commonly used to study the pathogenesis of influenza. Results: In human respiratory tract tissues, both H7 viruses attached to tissues from the upper and lower respiratory tract. In the nasal turbinates, trachea, bronchi, and bronchioli the viruses attached to ciliated epithelial cells. In the alveoli, both viruses attached to type I and type II pneumocytes and alveolar macrophages. Interestingly, in the ferret respiratory tract, both H7 viruses attached to ciliated epithelial cells in the nasal turbinates, but rarely to ciliated epithelial cells of the trachea, bronchi and bronchioli. In the alveoli, both H7 viruses attached to type I and type II pneumocytes. Conclusion: The attachment pattern of these emerging H7 viruses in the human respiratory tract is different from the attachment pattern of other avian influenza viruses, which rarely attach to tissues of the upper respiratory tract. Interestingly, this pattern was independent of the Q226L mutation in the receptor binding site, as both viruses showed a similar pattern of attachment. The attachment pattern of H7 viruses in the ferret respiratory tract differed from that in humans. With the caveat that virus attachment is only the first step in the virus replication cycle, these results suggest that the emerging H7N9 virus has the potential both to transmit efficiently among people and to cause severe pneumonia.

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Mild to moderate influenza A(H7N9) infections detected through China's national influenza-like Illness sentinel surveillance system

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Background: The “clinical iceberg” phenomenon, where there are usually many more infected cases than is apparent symptomatically and even less so registered in the clinical setting, is a common feature of influenza disease. While this is certainly true for interpandemic influenza and the 2009 influenza A(H1N1) pandemic, this appeared to be less substantial for the Dutch A(H7N7) outbreak, and with A(H5N1) being an acknowledged exception. It remains unknown whether the “iceberg” applies to the influenza A(H7N9) virus that emerged in early 2013 in China. While the majority of laboratory-confirmed A(H7N9) cases presented with a severe clinical picture to a hospital, a small number of laboratory-confirmed cases have been identified through the sentinel influenza-like illness (ILI) surveillance system nationwide. The objective of our study was to describe the clinical characteristics of the complete case series of A(H7N9) cases as of May 15, 2013, that were identified through routine testing by the ILI sentinel surveillance system. Materials and Methods: ILI sentinel surveillance in China is conducted through a network of 554 hospitals across the country, with the total number of outpatient and/or emergency department visits and the number of patients fitting the WHO standard ILI case definition reported weekly online to the China CDC, and 10-15 nasopharyngeal swabs collected from ILI patients each week for routine laboratory testing and subtyping. All A(H7N9) cases detected through the ILI surveillance system by May 15, 2013, were identified by cross-referencing the laboratory-confirmed A(H7N9) line list with the routine sentinel ILI surveillance system. Demographic and epidemiologic data were extracted from field investigation records, and clinical and laboratory data were obtained from medical chart review. Results: Five (3.8%) of a total of 130 laboratory-confirmed influenza A(H7N9) cases reported as of May 28, 2013, were detected through the routine ILI surveillance system. Four (80%) of them were male. Mean age was 13 (range = 2-26) years and none had any underlying medical condition. Exposure history, geographic location and timing of symptom onset were otherwise similar to the general cohort of all laboratory-confirmed cases to date. All patients experienced only mild or moderate disease with an uneventful course of recovery. Among them three (60%) were managed only as outpatients and all quickly recovered after 3-5 days, with nasopharyngeal swabs tested positive for A(H7N9) only after their full recovery. Two patients (40%) were hospitalized for treatment. One was a 4-year-old child from Shanghai who presented initially as an outpatient with fever and mild rhinorrhea to a routine sentinel clinic, and was admitted on the next day for oseltamivir treatment after his nasopharyngeal swab was tested positive for A(H7N9). The other was a 26-year-old man from Jiangsu who presented initially with fever and productive cough to a sentinel clinic, being given ceftazidime without improvement. He was admitted 4 days later with radiologic evidence of left-sided pneumonia, and started on oseltamivir and moxifloxacin. Both remained clinically stable with quick resolution of symptoms within 10 days. Conclusions: Our complete case series of A(H7N9) cases detected through the routine ILI surveillance system provide contrasting clinical presentations to the generally much more severe clinical picture of the majority of laboratory-confirmed A(H7N9) cases detected otherwise. Our findings provide indirect evidence of a substantial proportion of mild disease and support the existence of a “clinical iceberg” phenomenon in influenza A(H7N9) infections. For the clinician, our findings reinforce vigilance to the diverse presentation that can be associated with influenza A(H7N9) virus infections. Our results also suggest that large-scale community surveillance networks can be useful as a population-based sampling tool to enhance understanding of the full spectrum of disease, especially in the early phase of an evolving epidemic.

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