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Infectious Disease 2018: Differentiation of Subtypes for Influenza Surveillance Using a Peptide-Based Detection Platform (FluType): Henry Memczak-Stanford University School of Medicine, USA

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Introduction:

Influenza viruses are among the most common causes of human respiratory infections, and among the most significant because they cause high morbidity and mortality. Influenza outbreaks have apparently occurred since at least the Middle Ages, if not since ancient times. In the elderly, in infants, and in people with chronic diseases, influenza is associated with especially high mortality. In the United States, influenza results in approximately 200,000 hospitalizations and 36,000 deaths in a typical endemic season. In addition to annual winter outbreaks, pandemic influenza viruses occasionally emerge, as they have every 8 to 41 years for at least several centuries. Up to 50% of the population can be infected in a single pandemic year, and the number of deaths caused by influenza can dramatically exceed what is normally expected.

Since 1700, there have been approximately a dozen influenza A virus pandemics; in the past 120 years there were pandemics in 1889, 1918, 1957, and 1968. The 1957 pandemic caused 66,000 excess deaths in the United States. In 1918, the worst pandemic in recorded history caused approximately 546,000 excess deaths (675,000 total deaths) in the United States and killed up to 50 million people worldwide. It is very likely that influenza will return in pandemic form. Influenza B viruses can periodically cause large epidemics but do not cause pandemics. Influenza C viruses are endemic and sporadically cause mild respiratory disease. This review concentrates primarily on the pathology of influenza A viruses, by far the most important human influenza pathogens. The spectrum of influenza A histopathology is variable. Because pathology studies have emphasized autopsy material, only changes associated with lethal outcomes and predominantly late-stage disease have been well characterized. There is a broad spectrum of changes associated with influenza infection, varying with both clinical picture and length of the disease course before death. Coincident or secondary bacterial pneumonias are not only extremely common in severe influenza but also complicate the histopathologic appearance. Nevertheless, the spectrum of observed pathologic changes appears to vary little from pandemic to pandemic or in interpandemic years. What separates the 1918 influenza cases from cases seen in less severe pandemics and in seasonal influenza infections is not the spectrum of observed pathology in severe and fatal cases but the significantly higher case fatality rate and—in the 1918 pandemic only—an unusual age distribution of deaths. In 1918, many previously healthy young adults succumbed to fatal influenza infection, whereas the elderly had lower than expected fatality rates. In the past two pandemics and especially in interpandemic seasonal influenza cases, fatal cases tended to occur in people with underlying chronic illnesses or at the extremes of age .

Concern about the emergence of an influenza pandemic caused by a highly pathogenic avian influenza (HPAI) virus of H5N1 subtype makes reviewing the pathology of previous pandemics relevant. Unfortunately, only three autopsy examinations have been reported for individuals dying after H5N1 infection. Whether the typical spectrum of influenza pathology would be observed if additional pathology studies were performed remains unclear. It has been proposed that the pathogenesis of H5N1 influenza virus infection may feature a unique hypercytokinemia. Data also suggest that the H5N1 virus may replicate outside the respiratory tree. It is crucial for pandemic preparedness planning that additional careful and complete autopsy studies of H5N1 influenza viral infection be performed and reported to answer important questions about natural history, pathology, and pathogenesis.

Influenza is an acute respiratory disease characterized in its full form by the sudden onset of high fever, coryza, cough, headache, prostration, malaise, and inflammation of the upper respiratory tree and trachea. In most cases, pneumonic involvement is not clinically

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prominent. Acute symptoms and fever often persist for 7 to 10 days. Weakness and fatigue may linger for weeks. Influenza usually occurs in winter outbreaks or epidemics (in temperate climates). People of all ages are afflicted, but the prevalence is greatest in school-age children; disease severity is greatest in infants, the aged, and those with underlying illnesses. Croup (laryngotracheitis) can be a serious complication in small children. Influenza A and B viruses are the most common causes of influenza-like illness (ILI), but other pathogens also cause ILI, including influenza C viruses, parainfluenza viruses, respiratory syncytial viruses, and Mycoplasma pneumoniae. At the peak of an influenza epidemic, approximately one-third of isolates from patients with ILI will be positive for influenza A.

People with chronic pulmonary or cardiac disease, or diabetes mellitus, are at high risk of developing severe complications from influenza A viruses, which may include hemorrhagic bronchitis, pneumonia (primary viral or secondary bacterial), and death. Hemorrhagic bronchitis and pneumonia can develop within hours. Fulminant fatal influenza viral pneumonia occasionally occurs; dyspnea, cyanosis, hemoptysis, pulmonary edema, and death may proceed in as little as 48 hours after the onset of symptoms.

Influenza A viral replication peaks approximately 48 hours after inoculation into the nasopharynx and declines slowly, with little virus shed after about six days. The virus replicates in both the upper and lower respiratory tract. Even after the infectious virus can no longer be recovered, viral antigen can be detected in cells and secretions of infected individuals for several days. The diagnosis of influenza can be established by viral culture, demonstration of viral antigens, or demonstration of viral genetic material (in clinical specimens), or rises/falls in specific antibody titers in serum or respiratory secretions

Abstract :

The only cost-effective protection against influenza is vaccination. Due to rapid mutation continuously new subtypes appear, what requires annual reimmunization. For a correct vaccination recommendation, the circulating influenza strains have to be detected promptly and exactly and characterized regarding their antigenic properties. Due to recurring incidents of vaccine mismatches, there is a great need to speed up the process chain from identifying the right vaccine strains to their administration. The monitoring of subtypes as part of this process chain is carried out by national reference laboratories within the WHO Global Influenza Surveillance and Response System (GISRS). To this end, thousands of viruses from patient samples (e.g. throat smears) are isolated and analyzed each year. Currently this analysis involves complex and time-intensive (several weeks) animal experiments to produce specific hyperimmune sera in ferrets, which are necessary for the determination of the antigen profiles of circulating virus strains. These tests also bear difficulties in standardization and reproducibility, which restricts the significance of the results. To replace this test a peptide-based assay for influenza virus subtyping is developed. The differentiation of the viruses takes place by a set of specifically designed peptidic recognition molecules which interact differently with the different influenza virus subtypes. The differentiation of influenza subtypes is performed by pattern recognition guided by machine learning algorithms, without any animal experiments.

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