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Comparable Fitness and Transmissibility between Oseltamivir-Resistant Pandemic 2009 and Seasonal H1N1 Influenza Viruses with the H275Y Neuraminidase Mutation

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Introduction: Neuraminidase (NA) inhibitors are one of the limited options for the control of influenza. The H275Y NA mutation, which confers resistance to oseltamivir carboxylate, was initially considered to be of little clinical consequence due to limited detection of this mutation in field isolates prior to 2007-2008, when a globally spreading H275Y variant emerged. Oseltamivir-resistant A(H1N1)pdm09 viruses with the H275Y NA mutation has been reported since 2009 but have not replaced the oseltamivir-sensitive wild-type strains to date.

Objectives: We aim to evaluate the effect of the H275Y NA mutation on fitness and transmission potential of three antigenically representative influenza strains of H1N1 subtype circulated among humans from 1999 to present time.

Methods: We generated recombinant viruses of different hemagglutinin (HA)-NA combinations and compared their growth in differentiated human airway epithelial cells that naturally secrete mucin. The effects of the H275Y mutation on the NA enzyme activity of the seasonal and pandemic H1N1 viruses were determined using kinetic assays. The transmission potential of the recombinant viruses were evaluated using the ferret model.

Results: The H275Y mutation led to reduced NA enzyme activity, an decreased affinity for 3'-sialylactose or 6'-sialylactose substrates, and decreased infectivity in mucin-secreting human airway epithelial cells compared to the oseltamivir-sensitive wild-type counterparts. All H275Y variants of recombinant A(H1N1)pdm09 or seasonal H1N1 influenza viruses with different HA-NA gene constellations transmitted from inoculated ferrets to naïve direct contact or respiratory droplet contact ferrets, with the transmission efficiency minimally affected when compared to their wild-type counterparts.

Discussion: Our results suggest that the H275Y mutation in H1N1 influenza leads to minor reduction in viral fitness with its transmission potential being minimally affected in the naïve ferret model.

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Hemagglutinin-neuraminidase Balance Confers Respiratory-Droplet Transmissibility of the Pandemic H1N1 Influenza Virus in Ferrets

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Introduction: A novel reassortant derived from North American triple reassortant (TRsw) and Eurasian (EAsw) swine influenza viruses acquired sustained human-to-human transmissibility and caused the 2009 influenza pandemic. To understand the mechanism of the emergence of influenza pandemicity, it is essential to identify viral determinants that confer efficient transmission in humans.

Objectives: To evaluate the transmissibility of the pandemic H1N1 and its precursor swine influenza viruses in ferrets and to identify gene segments that confer to efficient respiratory droplet transmissibility.

Methods: Representative swine influenza viruses of different lineages were evaluated for direct-contact and respiratory droplet transmissibility in ferrets. Transmission is defined by detection of virus shedding from the naïve ferrets and sero-conversion. Plasmid-based reverse genetics was applied to introduce gene segments from pandemic H1N1 virus into selected precursor swine influenza virus to identify molecular determinants that confer transmissibility.

Results: All swine viruses studied were transmitted by direct contact with varying efficiency, respiratory droplet transmissibility (albeit inefficient) was observed only in the A/swine/Hong Kong/915/04 (sw915) virus, which is a TRsw-like that had acquired the M gene derived from EAsw and differed from the gene constellation of the pandemic H1N1 virus by the neuraminidase (NA) gene alone. Glycan array analysis showed that pandemic H1N1 virus A/HK/415742/09 (HK415742) and sw915 possess similar hemagglutinin (HA) receptor binding specificity and affinity for alpha2,6-sialosides. Introducing the NA from pandemic HK415742 into sw915 increased respiratory-droplet transmissibility; the NA of the pandemic virus possessed significantly higher enzyme activity than that of the sw915 or other swine influenza viruses.

Conclusions: Gene constellation and the HA-NA balance were the key determinants of the efficient human transmissibility of pandemic H1N1 viruses.

Implications: The results highlight the importance of continued swine influenza surveillance and the viral transmissibility evaluation in the ferret model for public health risk assessment.

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A Randomized, Parallel, Controlled Study to Evaluate the Role of Directly Observed Therapy Short Course-plus (DOTS-Plus) Versus DOTS for Retreatment of Pulmonary TB in Guangzhou

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Objectives: 1) To evaluate the outcomes and effectiveness in the retreatment of pulmonary TB by the use of conventional sputum culture and drug susceptibility testing (DST) in guiding chemotherapy under usual program conditions in Guangzhou and 2) study the factor(s) influencing outcomes in the retreatment of pulmonary TB under program conditions in Guangzhou. We hypothesized that the addition of conventional sputum culture and