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Impact of Umifenovir use on the reduction secondary bacterial pneumonia following influenza

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Pneumonia often occurs secondary to influenza infection and accounts for a large proportion of the morbidity and mortality associated with seasonal and pandemic influenza outbreaks. The antiviral drug umifenovir (Arbidol) is licensed in Russia for treatment and prophylaxis of acute respiratory infection including influenza A and B infection. In the present study, we investigated the efficacy of umifenovir or oseltamivir in a mouse model of secondary *S. aureus* pneumonia following A/California/04/2009 (H1N1) influenza virus infection. We also performed a clinical study on the effectiveness of umifenovir in reducing flu-associated pneumonia. Experiments in mice showed that oral treatment with oseltamivir (20 mg/kg/day) and umifenovir (40 and 60 mg/kg/day) improved survival in mice from 0% to 90%, significantly prolonged survival and abolished weight loss. The treatments also inhibited virus titer by ≥2 logs and viable bacterial counts in the lungs of mice. The lungs of mice treated with oseltamivir or umifenovir showed less-severe histopathologic findings compared to the control group. The observation case-control clinical study was set up in season 2010/2011 and 2014/2015 and included 5287 patients admitted to 88 hospitals with acute respiratory viral infections (ARVI) from 50 regions of the Russian Federation. The analysis showed that in high-risk groups of patients the incidence of bacterial complications (pneumonia) was higher than the average for the study population. Our observational studies suggest the benefit of early umifenovir treatment (i.e., within 48 hours after illness onset) in reducing pneumonia incidence in high-risk patients.

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Minimal requirements for high virulence of non-H5/H7 avian influenza viruses

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Avian influenza viruses (AIV) are classified as either low pathogenic (LP) or highly pathogenic (HP) due to their virulence in chickens. Highly pathogenic avian influenza viruses (HPAIV) exhibit a polybasic cleavage site (PCS) within the hemagglutinin (HA) protein and therefore the HA can be cleaved and activated by ubiquitous proteases causing severe systemic disease with high lethality. Naturally occurring HPAIV have always been of subtype H5 or H7 with very rare exceptions. Recently we showed that HPAIV can be created with other HA subtypes exhibiting an artificial PCS in a H5 HPAIV background and the introduction of a PCS within the HA in the parental background was not sufficient. Therefore, the objective of the study was to investigate the minimal requirement for exhibiting a highly pathogenic phenotype of non-H5/H7 LPAI viruses. Reverse genetics systems were established for LPAIV strains H4N6 and H8N4. Reassortants of LPAIV HA with artificial PCS and gene segments of a H5N1 HPAIV were generated and the virulence was ascertained in SPF chickens. In summary, the HPAIV H5N1 nucleoprotein (NP), neuraminidase (NA) and the matrix protein (M) segments conferred increased virulence. Whereas the impact on virulence of the NA and M gene segments differed, the NP gene of H5 HPAIV increased virulence in both H4 and H8 backgrounds. Furthermore, the impact of single NP amino acids was assessed.

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