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The Epidemiology, Diagnosis and Treatment of H5N1, H1N1 and H7N9

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On March 31, 2013, a novel avian viral (H7N9) infection was identified in Shanghai with fatal outcome [1]. Till May 10, 2013, 111 laboratory-confirmed H7N9 cases had been reported in Shanghai, Zhejiang, Jiangsu, Anhui, Henan and Beijing [2]; amongst which 27.0% had died [3]. It reminded the public of precedent H5N1 and H1N1 pandemics which had swept across the globe with substantial infection and mortality. In 1997, H5N1 pandemic was first proclaimed with 18 infections and 6 related deaths in Hong Kong [4,5]. It was gradually resolved to sporadicity via depopulation of birds and poultry but broke out yet again in 2003 to cause 424 confirmed cases and 261 deaths as of May 15, 2009 [5]. H1N1, a product of multiple assortments between avian, swine and human influenza viruses, initiated another pandemic in Mexico in 2009 which spread across the globe and resulted in 11034 cases and 85 deaths in 41 countries as of May 21, 2009 [6].

H5N1, H1N1 and the novel H7N9 are type A influenza viruses belonging to the RNA viral family Orthomyxoviridae. Unlike types B and C of the family, type A presents rapid evolution and variations in antigenicity, pathogenicity and host specificity capable of avian and mammalian infections. According to the antigenicity of Hemagglutinin (HA) and Neuraminidase (NA) molecules, type A viruses are subdivided into 16 HA subtypes (H1-H16) and 9 NA subtypes (N1-N9). Generally sporadic, introduction of a novel HA subtype in the human population through genetic reassortment or inter-species transmission may initiate an influenza pandemic. An infected individual may develop contagious respiratory conditions of influenza characterized by high fever, cough, headache, malaise and inflammation of the upper and lower respiratory tract. In severe cases, complications such as pneumonia, hemorrhagic bronchitis, multiorgan dysfunction, central nervous system involvement and death may result. Specifically, H5N1 viruses replicate mainly in the lower respiratory tract [7,8] and disease severity correlates directly with viral load to cause severe pneumonia, lymphopenia, hypercytokinemia and hyperchemokinemia [7-12]. Pulmonary manifestation of H1N1 infection varies between febrile upper respiratory tract infection, fulminant primary viral pneumonia and secondary bacterial pneumonia with Acute Respiratory Distress Syndrome (ARDS). The novel H7N9 infection, similarly, has been observed with fulminant pneumonia, respiratory failure and ARDS [9]. Among H1N1 and H7N9, rhabdomyolysis and encephalopathy, at midst other extrapulmonary manifestation, have been reported [13-15].

While clinical manifestation serves as a means of tentative diagnosis, confirmative tests should be implemented to differentiate the possibilities of other viral or bacterial infections. Basically, they include viral isolation, serological tests, rapid antigen tests and molecular tests [16-19], each possessing unique strengths and weaknesses. Viral isolation is the gold standard for diagnosis and takes advantage of viral replication in Madin-Darby canine kidney cells or other media to isolate viruses. Its application in routine diagnosis remains limited as an average input of 2-3 days in a biosafety level 3 laboratory is necessary to perform the propagation. In the preliminary discovery of H7N9, throat-swab specimens from suspected patients were propagated in the allantoic sac and amniotic cavity of 9-to-11-day old specific pathogen-free embryonated chicken eggs to isolate the pathogen [13]. Serological tests detect antibody response of a suspected patient which take days to develop but remain undetectable in fulminant cases. Rapid antigen tests, on the other hand, are commercialized antibody kits that detect influenza antigens within 20 minutes at high costs with little information about subtypes. Nonetheless, rapid antigen tests for H1, H3 and avian H5 subtypes have been developed despite a need for improved performance [20]. Comparatively speaking, molecular tests are the most sensitive and efficient diagnostic tools that confirm the presence of influenza viruses through amplification of target nucleic acids. They include reverse-transcription PCR (RT-PCR), real-time RT-PCR, nucleic acid sequence-based amplification, loop-mediated isothermal amplification (LAMP), microarray and pyrosequencing. RT-PCR and real-time RT-PCR are similar techniques, the latter yielding quantitative results, which detect the highly conserved M gene of type A influenza viruses and conserved regions of its HA gene. In spite of high start-up costs, real-time RT-PCR is widely utilized as first-line identification of influenza viruses due to its (i) readily available primer sequences; (ii) high sensitivity; (iii) quantitative results suggestive of prognostic significance. Currently, commercialized real-time RT-PCR assays have been developed for laboratory diagnoses of H5N1 and H1N1. In the discovery of H7N9, RNA was first extracted from throat-swab samples of suspected patients to perform RT-PCR for seasonal influenza viruses (H1, H3 or B), H5N1, severe acute respiratory syndrome coronavirus (SARS-CoV) and novel coronavirus. When such options were eliminated, self-designed primer and probe sets for H1 to H16 and N1 to N9 subtypes were used to identify viral subtypes [13].

Together with Neuraminidase (NA) inhibitors (oseltamivir, zanamivir, peramivir), adamantanes (amantadine, rimantadine), acting via M2 ion channel inhibition, serve as antiviral treatment against influenza viruses. In treating H5N1, adamantanes were found to be primarily resisted in Thailand, Cambodia and Vietnam. In view of such, oseltamivir was recommended as first-line treatment while oseltamivir phosphate or zanamivir as prophylaxis [21]. Nevertheless, 2 of 7 H5N1 patients in Vietnam had displayed signs of oseltamivir resistance during treatment, suggesting considerable resistance rates of the drug [22]. Furthermore, clinical experience has denied the survival advantage of oseltamivir and its efficacy has not been verified [8,10,23-25]. While delayed treatment could be partly blamed, late preliminary drug administration should not be discouraged because pharyngeal viral loads were found to be undetectable among surviving patients after drug usage in small case series [22]. In treating H1N1, NA inhibitors failed to present survival advantage but its early administration was associated with reduced likelihood of severe clinical outcomes [26].

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Alarmingly, a significant increase in oseltamivir-resistant H1N1 viruses have been reported globally, probably as a result of prolonged infection among immunocompromised patients [27,28]. To guide the choice of therapy, neuraminidase inhibition assays may be performed to detect suspected antiviral resistance mutations. However, as the tests can only be carried out on viral cultures while certain virus mutants may be selectively enriched via viral propagation in Madin-Darby canine kidney cells, authenticity is questionable. Currently, limited experience remains when laboratory studies have verified sensitivity of H7N9 to neuraminidase inhibitors (oseltamivir and zanamivir) and resistance against amantadine and rimantadine [29-31].

In summary, the aforementioned influenza pandemics have taught us valuable lessons in diagnostics and public health management. They have reminded us the importance of preparation for upcoming influenza pandemics which may strike anytime and anywhere at any degrees. It is thus our liability to equip with relevant knowledge and react quickly towards such crises when they next prevail.

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