Influenza is primarily a disease of shore birds and aquatic birds, with sea mammals, horses, pigs, poultry and humans as incidental hosts. Human influenza is a disease with two faces. Seasonal influenza is endemic with annual winter peaks. Attack rate could be 25-30% but case-fatality rate is relatively low and mostly affects the very young, the very old, and those with chronic sickness. Pandemic influenza occurs once every few decades and may be associated with a high case-fatality rate. Deaths typically involve all age groups and previously healthy people are not exempt.

The influenza virus
Influenza virus belongs to the family orthomyxoviridae and is classified into types A, B, and C. Influenza A is the most important one as it causes frequent epidemics and occasional pandemics. Influenza B causes epidemics but not pandemics, and influenza C only causes mild disease in humans.

The influenza A virion consists of a protein coat enveloping 8 single stranded, negative-sense RNA genes coding 11 proteins. Matrix protein 1 (M1) forms the main structure of the protein coat. Matrix protein 2 (M2) is located within the protein coat and is a channel enabling exchange of ions between the virion and the environment. Protruding from the protein coat are two surface proteins: the spike-like haemagglutinin (HA1, HA2) and the mushroom-like neuraminidase (NA). Haemagglutinin attaches to sialic acid receptors on host mucosal cells to initiate an infection. It is divided into 16 antigenic subtypes. Neuraminidase frees progeny viruses from attachment to the original host cell so that they can go forth to infect other host cells. It is divided into 9 antigenic subtypes. Inside the virion is a nucleoprotein (NP) which together with the RNAs forms the structure of the genes. The NP gene is also involved in many viral functions including interaction with host proteins thereby playing a role in host specificity. The RNA-polymerases (PA, PB1, PB2) are responsible for replication of the viral RNAs, while the non-structural proteins (NS1, NS2) are believed to interfere with host defences such as interferon production.

Influenza viruses do not have proofing enzymes for RNA replication so that "mistakes" are very common. It was estimated that a nucleotide change happens as often as one in ten thousand. Since there are approximately ten thousand nucleotides in the influenza genome, every newly formed influenza virion has a good chances of having at least one mutation. While most mutations are either meaningless or deleterious, some do confer survival advantage via a number of possible mechanisms. This constant change (antigenic drift) explains why humans do not have lasting immunity against the influenza virus. Another mechanism for emergence of new influenza strains is for two different strains to infect the same host cells with exchange of genes during assembly of new virus particles. Such genetic reassortment results in more dramatic changes and is associated with "antigenic shift".

Aquatic and shore birds strike a much better balance with influenza viruses, with the birds not getting sick and the viruses hardly changing over a century. This "evoluntionary stasis" led biologist to believe that these birds have been infected with influenza viruses for a very long time, and is the "primordial host" of it.

Seasonal influenza
Seasonal influenza is endemic and often reaches epidemic proportions in winter months. In Hong Kong and other sub-tropical and tropical regions there may be an additional summer peak, or the seasonal pattern may be totally irregular. In 1968 an H3N2 subtype replaced the previously circulating H2N2 as the dominant influenza A subtype for seasonal influenza. In 1977 H1N1 returned and instead of replacing H3N2 co-circulated with it up to the present day. Along with influenza B there are thus 3 subtypes of influenza regularly infecting humans.

The incubation period of influenza is 18 to 72 hours. Virus shedding can precede symptom onset by up to 24 hours, and lasts up to 5 days after symptom onset. Virus transmission is mainly through large droplets and fomites but there is increasing evidence for aerosol transmission which raises the advocate that N95 masks and not surgical masks should be used for infection control involving influenza. With the above features, it is easy to appreciate that influenza can spread very quickly in dense human populations, and is the ideal pathogen for severe epidemics.

The onset of symptoms is typically rapid, with fever, chills, cough, and prominent systemic symptoms such as malaise, headache, and myalgia. Although influenza can often be distinguished from common cold, infections by some other viruses like respiratory syncytial virus and parainfluenza viruses may give very
similar clinical features. Utilising data from multi-national drug trials, Zambon et al found that using a clinical diagnostic criterion of fever ($\geq 37.8 \, ^\circ \mathrm{C}$ for $< 65$ year old and $\geq 37.2 \, ^\circ \mathrm{C}$ for $\geq 65$ year old) plus any two of headache, myalgia, sore throat, and cough, $77\%$ of laboratory-confirmed influenza were correctly identified during influenza seasons$^6$. Sore throat however was found to be negatively correlated, and the same finding was reported by similar studies$^7,8$ so it was concluded that sore throat is a negative predictor of influenza and should be dropped from the diagnostic criteria. Outside influenza seasons, the low influenza prevalence would render such diagnostic criteria much less useful. Furthermore, it has been shown that for elderly people, infection by different respiratory viruses were clinically indistinguishable$^9$.

With the non-specific clinical features, laboratory confirmation of influenza is highly desirable for decisions on treatment and isolation as well as for epidemiological surveillance. Serology test using paired serum for haemagglutination-inhibition study as well as viral culture are gold standards, but both require weeks for results to become available so they are more suitable for epidemiology and research. Reverse-transcription polymerase chain reaction (RT-PCR) can provide results within a few hours and a number of studies have found that it identified more true-positive samples than either serology or virus culture$^{10,11}$. These findings led some investigators to consider that RT-PCR should be the gold standard for the diagnosis of influenza$^6$. However, RT-PCR can only be done in the hospital setting. Other rapid tests such as Directigen FluA+B employ an enzyme immunoassay technology and can be used in the clinic setting. A local study on nasopharyngeal aspirates mainly from children $< 6$ years old found that the sensitivity, specificity, and positive and negative predictive values of the Directigen FluA+B test for influenza virus type A were $96\%$, $99.6\%$, $96\%$, and $99.6\%$, respectively, and for influenza virus type B they were $87.5\%$, $96.8\%$, $80\%$, and $98\%$, respectively$^{12}$. Others have reported variable results and one study reported a sensitivity of only $43.83\%$, although specificity was excellent$^{13}$. Decreased sensitivity is seen in adult patients as well as use of specimens other than nasopharyngeal aspirate$^{10}$. Other rapid tests for influenza A and B such as Binax NOW and QuickVue have similar sensitivity and specificity to Directigen$^{14,15}$.

Beside bed-rest, adequate fluid intake, and symptomatic relief, antivirals have recently been the focus for influenza treatment. Amantadine was introduced soon after the Hong Kong flu of 1968. It is active against influenza A but ineffective for influenza B. Its main antiviral mechanism is believed to be interference of M2-protein mediated ion transport$^{16}$. An early study found that the mean duration of fever was 46.6 hours for the amantadine-treated group compared to 75.1 hours for the placebo group ($p<0.01$) if amantadine is taken with 48 hours of symptom onset. There was also a trend towards shortened mean duration of symptoms for the amantadine group not reaching statistical significance$^{16}$. However, amantadine has significant gastrointestinal and central nervous system side effects, and resistance involving M2 mutations develop easily.

DANA (2-deoxy-2,3-dehydro-N-acetyl neuraminic acid) was a molecule designed to form a complex with the active ‘pocket’ of the influenza neuraminidase in the early 1990s$^{17}$. Improved visualisation of the 3-dimensional structure of neuraminidase led to modifications of DANA resulting in the introduction of zanamivir followed by oseltamivir in 1999. The former is in the form of capsules for inhalation while the latter are capsule for oral intake. Both formulations, if taken within 48 hours of symptom onset, can reduce duration of fever and duration of symptoms, and reduce the rate of complications and need for antibiotics$^{18-22}$. Both formulations have also been shown to prevent influenza in household contacts$^{23-25}$. Oseltamivir is more popular since oral intake is more preferred by patients, but there is recent concern on development of drug resistance$^{26}$. However, since the mechanism for oseltamivir resistance does not affect the action of zanamivir$^{27}$, resistance to the latter has so far not been reported. With the marginal benefit of neuraminidase inhibitors on seasonal influenza and the increasing risk of drug resistance, it has been proposed that the neuraminidase inhibitors should be reserved for pandemic influenza$^{28}$.

The tri-valent influenza vaccine has an efficacy of 70-90% in adults aged $< 65$ years in influenza seasons in which the circulating strains are well matched to the vaccine strains, and is 38-52% when the circulating strains are significantly different from the vaccine strains$^{29}$. Elderlies have a poorer antigenic response and the vaccine efficacy has been estimated to be only 17-53% depending on circulating viruses$^{30}$. For the winter of 2006-07, the Advisory Committee on Immunisation Practices has recommended the following vaccine composition: A/New Caledonia/20/1999 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like antigens$^{29}$. Target groups for vaccination include:

- Persons at high risk for influenza-related complications and severe disease, including
  - children aged 6-59 months,
  - pregnant women,
  - persons aged $\geq 50$ years,
  - persons of any age with certain chronic medical conditions; and
- Persons who live with or care for persons at high risk, including
  - household contacts who have frequent contact with persons at high risk and who can transmit influenza to those persons at high risk,
  - health care personnel on all health care settings$^{31}$

The importance of administering 2 doses of influenza vaccine for children aged 6 months to $< 9$ years who were previously unvaccinated was highlighted$^{32}$.

Pandemic Influenza

There were about three influenza pandemics each century for the last 3 centuries. The “Spanish flu” of 1918-19 was probably the worse pandemic the human race has ever seen, and killed some 40-50 million people worldwide$^{32}$. The 1997 outbreak of avian influenza in Hong Kong caused tremendous concern not only because it was the first time that a totally avian influenza
In order to control pandemic influenza at source, we need first of all to know how pandemic influenza strains come about. Previously it was believed that pandemic strains resulted from genetic reassortment between an avian influenza strain and a human influenza strain, with the pig being the "missing vessel". While the 1957 and 1968 pandemic influenza strains were in reassortants, evidence for the pig being the mixing vessel was lacking. Furthermore, the 1918 pandemic strain is found to result from adaptive mutation of an avian virus without reassortment with human viruses. Added to recent reports of direct infection of humans by various avian influenza viruses it is now believed that such infections have been occurring regularly and frequently for a long time. The pool of avian influenza viruses undergo continuous reassortment within their natural hosts and is a potent source for pandemic virus candidates. It is thus very important for surveillance systems to pick up highly pathogenic avian influenza viruses in both birds and humans quickly and to control their onward passage by culling of infected flocks and isolation of infected humans. Should a pandemic start, effective models using antivirals and social-distancing measures are found to result from adaptive mutation of an avian virus because the only hurdle it has to overcome is the ability to infect a new host. Therefore, an efficient vaccine should be considered useful at this juncture. General medical, nursing, and respiratory support would likely be the mainstay of treatment.

References