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<th>Avian influenza A/H5N1 virus: Management in human and bird</th>
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The high mortality of over 50% in Hong Kong patients with pneumonia caused by the influenza A/H5N1 virus in 1997 was found to be quite consistent in subsequent outbreaks in South-East Asian countries.\(^1,2\) Our initial clinical observation was that this disease was not simply a viral pneumonia, and that all other major organs could be affected due to a cytokine storm caused by virus-induced aberrant immune activation. Fatalities were often associated with severe lymphopaenia, pancytopenia, impaired coagulation profiles, impaired liver and renal functions in addition to oxygen desaturation on admission. Besides diffuse alveolar damage in the lungs, lymphoid atrophy and necrosis were prominent in the spleen and lymph nodes with reactive haemophagocytosis, also evident in bone marrow.\(^3\) Unlike seasonal influenza caused by the human virus, which usually can only be isolated in the respiratory secretions, the A/H5N1 virus can also be found in the blood, faeces, and cerebrospinal fluid.\(^4\) Thus, this so-called cytokine storm could be the end result of uncontrolled systemic viral infection as in severe septic shock due to poorly treated Gram-negative bacteraemia.

Human vaccination to prevent the A/H5N1 virus is not commercially viable because of the low number of human cases and the rather rapid viral antigenic drift. The option of antiviral therapy is very limited, because resistance to adamantanes is widespread in A/H5N1 isolates from Vietnam and Thailand. Zanamivir is likely only to be useful for prophylaxis in health care workers, because it is delivered by inhalation and not expected to reach therapeutic concentrations in extrapulmonary tissues or hypoventilated areas of lung consolidation. Treatment with oseltamivir did not obviously result in improved survival, but there was a trend towards better survival if given early in the course of illness.\(^5\) Though the poor response may have resulted from delayed treatment initiation, other factors might be equally important. These include: the non-specific initial manifestations of A/H5N1 infection, the high initial viral load, poor oral bioavailability of oseltamivir in seriously ill patients, lack of a parenteral preparation, and the ready emergence of resistance. Since the lymphopaenia and serum pro-inflammatory cytokine levels correlate directly with the viral load in respiratory secretions,\(^6\) it is also reasonable to consider giving immunomodulators to dampen the cytokine storm. However, the use of steroids did not improve survival and was associated with significant complications such as hyperglycaemia and superinfection.\(^7\) In fact, after knockout of pro-inflammatory chemokine and cytokine genes or treatment with steroids, A/H5N1 virus–infected mouse models showed no significant improved survival.\(^8\) Due to the low incidence of this important disease, randomised controlled clinical trials are unlikely to be conducted. However, data from mice models suggest that high dose of oseltamivir therapy prolonged to more than 8 days,\(^9\) combination of oseltamivir with amantadine,\(^10\) and use of high titres of neutralising monoclonal antibody or convalescent plasma, may improve survival.\(^11\)

Recently, we combined the systemic administration of zanamivir with the COX-2 inhibitor celecoxib and mesalazine to treat mice inoculated with a high dose of A/H5N1 virus.\(^12\) Despite delayed therapy initiation of up to 48 hours after inoculation, this combination significantly reduced the viral load, production of pro-inflammatory cytokines, chemokines, leukotrienes, as well as mortality. The inhibitory activities of these non-steroidal anti-inflammatory agents against the pro-inflammatory response, together with the anti-apoptotic activities of the aminosalicylate, reduced cell death and tissue damage in the host. The concomitant use of an effective antiviral is essential, not only to limit the extent of viral replication that drives the cytokine dysfunction triggered by the infection, but also to counteract the possible increase in viral load after COX-2 inhibition. Notably, these drugs are widely available and intravenous zanamivir has been used in humans with little in the way of side-effects.\(^13-15\)

However, prevention is always better than cure. No developed nation in the world is really prepared for a 1918-like pandemic influenza. In the absence of efficient inter-personal spread of the A/H5N1 virus, preventing major outbreaks of human infection relies on controlling its endemicity in poultry. This entails prevention and prompt management of outbreaks in poultry, separation of poultry from humans to minimise transmission to them, and proper management of occasional human infections. At the height of the 1997 outbreak in Hong Kong, 20% of the poultry in wet markets were infected by the virus. Control of the outbreak ensued after culling of all the 1.5 million poultry throughout Hong Kong. Sale of live ducks and geese in wet markets was banned, as these birds can shed the virus asymptptomatically. Biosecurity measures in local farms were strictly enforced, and a bi-weekly rest day with cleansing of all the poultry stalls was introduced to interrupt the transmission cycle in wet markets. Vaccination against influenza A/H5 infection was required for all poultry in local farms and farms supplying live poultry to Hong Kong from Mainland...
China. These stringent measures appeared successful in preventing the incursion of the virus into local farms and markets for several years. Unfortunately, we cannot prevent the expected antigenic drift which will overcome the protection conferred by the poultry vaccine and thus require changes in vaccine according to the dominant endemic viral strain at that time. Complete elimination of illegal poultry imports into Hong Kong from unregistered farms in the Mainland is unlikely to be successful. Moreover, chicken stalls in wet markets may be regarded as mini-farms, where biosecurity measures comparable to those imposed on recognised farms are impossible to implement. Thus, the final answer depends on central slaughtering, which eliminates any potential contact of live poultry with the general population. In the interim before central slaughtering is launched, daily culling of all unsold chickens can be expected to stop viral shedding from newly infected chickens. The latter may not stay in the market long enough to exceed the incubation period for viral shedding. However, such measures cannot stop viral shedding from illegally imported infected chickens.

Control of avian influenza outbreaks in poultry in developing countries poses even more formidable problems. The rising demand for meat protein associated with the improving open-door economy in South-East Asia is responsible for a tremendous increase in poultry farming. Regrettably, no corresponding improvement in the biosecurity measures have followed in the ensuing prolifigation of farms and markets, and over half of such poultry are reared in backyard premises. Theoretically, country-wide veterinary and virological surveillance of birds, perimetric depopulation of infected zones, and targeted immunisation of poultry with correct vaccines could all be helpful. Other potentially useful measures include: segregation of poultry species, regular moratoria of poultry in the markets, and the implementation of biosecurity and hygienic practices in farms, markets, and at a personal level might also help to control poultry pandemic. How many of these measures are practicable is questionable. Alternatively, lesser scale interventions at the district level can be considered in response to local virus detection even without evidence of excess poultry deaths, since virus shedding is common in asymptomatic water fowl. To reduce the environmental viral load and therefore the risk of re-infection of farmed poultry, a planned one-off moratorium of 3 weeks during the hottest months of the year may be an important measure, as shown by mathematical modelling. Backyard farms will then be re-populated by hatchlings from virus-free chickens and minor poultry to ensure a virus-free environment. Universal immunisation against avian influenza of all poultry in backyard farms is not feasible, and hence immunisation should be preferentially targeted to ducks, geese, and chickens in industrial farms. Free grazing of ducks and geese outside the pens should only be allowed if the birds carry adequate titres of neutralising antibodies against H5.

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A/H5N1禽流感病毒：人和禽的處理

1997年香港因A/H5N1流感病毒導致亞洲禽的死亡率超過50%，而東南亞國家後來的情況與此相仿一致。據我們的初期觀察，這種疾病並不僅僅是一種瘟疫性疾患，由這種病毒引起的免疫系統異常活躍而導致的細胞激素風暴，也可能影響到所有其他重要器官。致命的原因，往往與人類及動物細胞內環境改變有關，如紅細胞減少、凝血狀態異常，肝和腎功能損傷等，以及氧化應激反應等。由於這種細胞激素風暴的發病機制並不明確，通常只能在後遺症期細胞內的人類病毒所導致的細胞激素風暴因不同，A/H5N1病毒可以在血液、臍帶和臍液中找到。因此，這種細胞激素風暴並非一種失調的細胞激素風暴，表現為正常細胞激素風暴不適時延緩引起的敗血症狀態。

由於人類的感染個案不多，以及抗病毒的迅速演變，所以難以預防A/H5N1病毒的感染也並不符合商業原則。抗病毒治療的方法不多，因為禽流感基因分離出來的A/H5N1對於金鶏並沒有抗藥性。扎那米韋只有有利于護理人員用作預防，因為這種藥物是通過口腔吸入，而且不能夠被被肺炎過程中細胞變異了或換取不足的肺部或肺周組織，而奧司他韋治療並沒有明顯提高患者存活的機會，而僅在發病初期使用這種藥物，則存活的機會較大。對於奧司他韋反應不佳是延緩開始用藥所致，但其他因素也可同時重要な。因此，包括A/H5N1感染病例在內治療上以抗病毒療法為主，確定禽流感病毒的感染率及治療期間產生的抗藥性。由於細胞細胞減少和促進促炎細胞因子的水平，與呼吸道出現的病原體之常見感染，可以於抗病毒藥物之外，只有免疫療法以減低細胞激素風暴，也是合理的治療方案。然而，使用類固醇沒有提高患者的存活機會，反而會引起血壓過高和重複性發作。性質上，受病毒感染被剝除了促炎因子和細胞因子的實驗鼠，或接受類固醇處方前，存活機會也沒有顯著提高。由於這種重要疾病的病發率高，不大可能進行體外的監控及療程。不過，從實驗鼠得到的顯示，較高劑量的奧司他韋和延長至8天以上治療的奧司他韋及金剛烷胺的結合使用，以及使用高密度和單倍體抗體或抗血清，或可提高病者的存活機會。近期，我們把扎那米韋用於肌肉注射治療受禽流感A/H5N1病毒的實驗鼠，再配合COX-2抑制劑塞洛普布和美沙拉凝。均未治療至無禽流感病毒後48小時才開始，這種治療療法顯著減低受禽流感細胞因子、趨化因子和白三烯的產生，以及動物的死亡。這些類固醇抗炎藥對抗炎反應的抑制力，加上氯基水楊酸膽固醇的抗炎力，減少了動物的細胞死亡和組織損傷。自結核感染後的病毒複製，引發細胞功能障礙，是必須伴隨使用有效的抗病毒藥物，以限制病毒的複製程度。此外，這些藥物可用以抑制COX-2抑制作用病毒量的上升。有應該指出的是，這些藥物供應充足，而且扎那米韋靜脈注射在人類內副作用不詳。