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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.\textsuperscript{5,2} 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.\textsuperscript{5} 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.\textsuperscript{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 only likely 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.\textsuperscript{7} 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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} 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,\textsuperscript{9} combination of oseltamivir with amantadine,\textsuperscript{10} and use of high titres of neutralising monoclonal antibody or convalescent plasma, may improve survival.\textsuperscript{11} Recently, we combined the systemic administration of zanamivir with the COX-2 inhibitor celecoxib and mesalamine to treat mice inoculated with a high dose of A/H5N1 virus.\textsuperscript{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.\textsuperscript{15-16}

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 profligation 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. 8 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：人禽共患

1997年香港因A/H5N1流感病毒导致禽流感的病人，死亡率超过50%，而东南亚国家的病者情况与此相当一致。我們的初期觀察，這種疾病並不僅僅是一種病毒性流感，由病毒引發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，往往與炎症反應有關，細胞細胞內，造成組織嚴重減速、全血細胞減少、凝血樣態異常、肝和腎功能異常，以及氧和pH下降有關。除了廣泛的肺泡受損外，淋巴系統和腸胃等受損的情況在有活性作用的病毒被吞噬細胞的染色和檢測中，乃至在骨骼中，相當顯著。而通常只能存在於呼吸道分泌物中的人類病毒所導致的急性溫度反應，A/H5N1病毒可以在血液、蛋白和細胞中找到。因此，這種所謂的細胞激素風暴不逐是不問疾病的細胞激素風暴反應。情況正如革蘭氏陰性菌細胞壁醇質不常引致的敗血症一樣。

由於人類的感染個案不少，以及病毒抗原的迅速變種，所以上確診A/H5N1病毒的病者並不適合商業原則。抗病毒治療的方法不多。因為越南和泰國分開出來的A/H5N1對於金剛酸有較好的抗藥性。扎那米齊有著優於維蓋爾二氨的優勢，因為它能擴展其口腔吸入，而不能夠對抗被肺炎過病例變了或損傷不夠的肺部或肺外組織。而奧司他韋治療治療沒有明顯提高病者生存的機會，但倘若在發病初期便使用這種藥物，則存活的機會亦大。

由於奧司他韋反應不佳是在延遲開始使用所致，但其他因素亦可影響重要。這些因素包括A/H5N1感染初期病徵不明確、初期病徵量大，嚴重病者口服奧司他韋的吸收率低於未經靜脈腫注的方劑，以及治療期間產生的抗藥性。由於靜脈腫注細胞減少和促進細胞因子的水平，與貼膜細胞細胞的病毒量直接相關，所以給予抗病毒藥物之外，加入免疫調節劑以減少細胞激素的協助，也是合理的處理方法。然而，使用類固醇沒有提高病者的存活機會，反而會引起血糖過高和重複感染等併發症。事實上，受病毒影響被剝除了促炎因子和細胞因子的病者，或接受類固醇處方後，存活機會並沒有明顯提高。由於這種重要疾病的發病率低，不太可能進行隨機的監控試験。不過，從實驗設計得到的顯示，較高劑量的奧司他韋和延長至8天以上的治療期、奧司他韋與金剛酸的結合使用，以及使用高濃度和單獨劑量或重複血漿，或提高病者的存活機會。近期，我們把扎那米齊和脈衝注射治療受A/H5N1病毒的實驗鼠，再配合COX-2抑制劑塞洛昔芬和布洛芬藥。當這種治療延緩至病毒注射後48小時才開始，這種醫療法顯著減少了病毒量、細胞因子、趨化因子和白三烯的產生，以及動物的死亡。這些非內固醇抗炎劑對抗炎反應的抑制力，加上高壓脈衝脈衝的抗關節力，減少了動物的死亡和組織損傷。由自然感染併發症的病毒複製，引致細胞功能障礙，因此必須伴隨使用有效的抗病毒藥物，以限制病毒的複製程度。除此以外，這些藥物也用以抗衡COX-2抑制作用後病毒量的上升。還應該注意的是，這些藥物供應充足，而且扎那米齊靜脈注射在人體內副作用不多。

預防永遠勝於治療。但世界上沒有已發達國家真正為1918年那樣的流感做好準備。但A/H5N1病毒還沒有出現有效的人傳人之前，預防人類感染大規模的措施，主要是監控病毒發現地點、預防和迅速處理家禽的爆發、人禽分離減少禽類傳染人的可能，以及適當處理人類的禽流感感染。1997年香港禽流感高發期，浣腸市場205家禽受感染。控制措施是宰殺香港全部150萬隻家禽；濕場市場禁活禽飲食，因為這些家禽可以在沒有病徵的情況下排放病毒；本地農場需執行生物安全措施；濕場市場禽類須每兩周實施一天清潔消毒；供應家禽的本地本地和大農場均須進行A/H5流感防疫注射。這些嚴格的措施數年來有效防止了病毒入侵本地農場和市場。可惜，預防的抗原變異無法阻止，而很可能導致家禽禽類的病毒保護力下降。另外，非法入口的家禽之中可能有來自大陸走私農場的受感染家禽，但要完全消滅這些非法入口亦相當困難。更重要的是，濕場市場的活禽業種實際上是隻小農場，由於空間所限，不可能實行農場的生物安全措施。因此，最後的落敗是讓在中央屠宰之上，有者這樣才可避免活家禽與公眾接觸。在中央屠宰鼠實行之前的過渡期，灑落不過過的低的餵食和阻止新感染家禽的病毒排放，避免病毒在這個都市中長期與發揮一體。這樣，這種不能防止已受感染的非法入口禽隻的病毒排放。

發展中國家控制禽禽類禽流感，面對更為艱難的問題。東南亞的經濟不斷改善，帶來養殖業肉制品需求的不斷上升，為了應付這些需求，只有大量增加家禽飼養。可是，農場和市場的生物安全措施卻沒有相應改善，而半數禽類是在家禽的農場上飼養的。理論上，全國範圍的禽類和病毒監控，在疫區周邊宰殺可受感染的家禽，使用適當的疫苗作防疫，分隔禽類，市場短期禁止售賣家禽，在農場、市場和個人層面實行生物安全和衛生措施，凡此種種皆可控制這種禽類禽流感。

但在發展中國家這些措施卻往往很少能夠實行。如果在病毒檢測中沒有過量的家禽死亡，則在地裏層面上可以考慮採取比較小的措施，因為病毒排放在無症狀的家禽中相當普遍。為了降低環境的病毒量，從而減少農場家禽再次感染的風險，可以不斷地對高風險家禽進行病毒採集，每次按照數倉模型計算的結果，在年中高發的月份一次或兩次即可開始，也許是一種重要的措施。然後病毒當在農場的標本上塗抹新飼養來自無病毒雞隻和次級家禽的鴨，以確保環境不受病毒污染，給後院農場的禽類做全面的禽流感疫苗工作並不可行。因此，免疫療法應針對工業農場的鴨、鵝、雞。而只有在這些禽類帶有足夠濃度的抗H5N1病毒中和抗體的時期，才可允許飼養在欄外自由走動。