Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

physician and, in the Common Cold Unit's days, industry provided most of the experimental antiviral compounds for testing, while contributing to vaccine production and testing.

The report is good and its publication timely, but its content is too general and in parts is outdated.

Challenge studies are difficult but vital, let us not lose this opportunity for advancing our understanding, and making sure no-one is exposed to microbes unnecessarily.

Tom Jefferson
Cochrane Vaccines Field, 00061 Anguillara Sabazia, Rome, Italy
Toj1@aol.com

I dedicate this Comment to the memory of Dr David Tyrrell. I declare that I make an income from doing systematic reviews.

1 Microbial Challenge Studies of Human Volunteers. A guidance document from The Academy of Medical Sciences. May, 2005. London: Academy of Medical Sciences, 2005.
2 Tyrrell DAJ. The origins of the Common Cold Unit. *J R Coll Physicians Lond* 1990; **24:** 137–40.
3 Thompson KR. Harvard Hospital and its volunteers: the story of the Common Cold Research Unit. Warminster, UK: Danny Howell Books, 1991.

H5N1 influenza pandemic: contingency plans

The current epidemic of the highly pathogenic H5N1 strain of avian influenza, with a mortality of 58%, appears relentless in Asia, particularly in Vietnam and Thailand.[1] Although inefficient, there is some evidence of human-to-human transmission for the H5N1 virus.[2] A possible catastrophic pandemic could, therefore, emerge should re-assortment of viral antigens occur resulting in a highly infectious strain of H5N1. Influenza pandemics in 1917–18, 1957–58, and 1968–69 have already caused approximately 15, 4, and 0·75 million deaths worldwide, respectively.

A vaccine for H5N1 will not be available in the foreseeable months. Even if pharmaceutical manufacturing begins soon after an outbreak, there would not be a sufficient supply for the countries most in need—ie, the Asian nations. Antiviral drugs are consequently the only specific treatment, pending availability of effective vaccines. These include M2 inhibitors (amantadine and rimantadine), which are ineffective against H5N1 in vitro, and the neuraminidase inhibitors (oseltamivir and zanamivir).[3] The neuraminidase inhibitors reduce the severity and duration of symptoms, and prevent clinical influenza as post-exposure and seasonal prophylaxis.[4] Influenza contingency plans by the WHO and most governments generally advocate detection, isolation, staff protection, and the start of antiviral treatment for patients, and their contacts.[5] Many governments, including those of Hong Kong, Thailand, Singapore, Malaysia, and Korea, have already stockpiled, at a very substantial expense, vast quantities of oseltamivir to prepare for an outbreak.[5]

Nonetheless, the efficacy of neuraminidase inhibitors, even for non-H5N1 influenza A in healthy people and taken within 48 h of disease onset, is only slight (table).[6–11] The use of oseltamivir in five of the ten cases reported in Vietnam did not show any obvious clinical efficacy, and the mortality was 80% in this cohort.[12] The two neuraminidase inhibitors, oseltamivir and zanamivir, have not been directly compared in controlled trials. Their pharmacological properties are compared in the table.[6–11] Although both have similar efficacy, zanamivir has fewer adverse reactions, and a favourable resistance profile. The resistance factor would be an important consideration in a pandemic situation. The reasons for zanamivir not being chosen for stockpiling might include concern that young children and patients with intellectual or coordination impairments would not be able to inhale zanamivir properly, although there are novel ways of giving the drug to children.[13] The occurrence of bronchospasm and reduced lung function is very rare, and patients with asthma and chronic obstructive pulmonary disease (COPD) seem to tolerate inhalation of zanamivir as well as the placebo.[14] The inhaled flow rate needed to give the custom-designed inhaler for zanamivir (49–110 L/min)

	Zanamivir	Oseltamivir
Age approved for prophylaxis[6,7]	>5 years	>13 years
Age approved for treatment[6,7]	>5 years	>1 year
Renal impairment[6,7]	No dose adjustment required	Adjustment if creatinine clearance 10–30 mL/min
Hepatic impairment[6,7]	No dose adjustment required	Safety not established
Reduction of influenza symptoms[8,9]	By median of 1·5 day	By median of 1·3 day
Adverse reactions[6,7]	Allergy—very rare Bronchospasm and dyspnoea—very rare Rash and urticaria—very rare	Nausea 7·0–10·7% Vomiting 2·1–8·0% Diarrhoea 3·2–5·5% Bronchitis 0·7–3·7% Headache 1·6–20·1% Fatigue 0·8–7·9%
Frequency of drug resistance after treatment[10,11]	None reported	1·3 and 8·6–18·0% in adults and children, respectively

Table: **Comparison of pharmacological properties of neuraminidase inhibitors**

is similar to that for accuhaler (30–90 L/min), and turbohaler (60–90 L/min), which are popular dry-powder inhalation devices used by many asthmatic and COPD patients, even during exacerbations.[15,16] Therefore governments should also consider stockpiling zanamivir as an anti-influenza agent in their pandemic plans. Actual logistics for giving out antivirals to patients and close contacts need to be efficient and completed within 48 h. It seems more appropriate for community-based health-care personnel or even pharmacists, rather than hospital-based health-care workers, to handle such procedures.

Governments and health agencies should also consider planning for clinical trials, for instance a combination of both neuraminidase inhibitors, with or without other potential novel drugs, such as short-interfering RNAs and interferon.[3] These trials, if initiated at the early stages of a pandemic, could provide useful information for further patient and outbreak management in later stages. The geographic location of vaccine manufacturers in developed countries would also delay poorer Asian nations from obtaining the updated influenza vaccine. Perhaps vaccine and neuraminidase inhibitor manufacturing activities should also begin in Asia to deal with such deficiencies. The ethics of maintaining drug patents in a potential worldwide catastrophe is questionable. Epidemiological modelling suggests that influenza is more infectious than severe acute respiratory syndrome, and that severe acute respiratory syndrome infection control measures might not be adequate for a pandemic of influenza.[17] There will, therefore, be an overwhelming strain on health-care workers and hospitals in an H5N1 pandemic, and staff could be rapidly demoralised and degenerate into deserters, if colleagues develop hospital-acquired H5N1 infection, especially if not given adequate intensive-care unit treatment.[18] Protection of core personnel should also be planned to underpin recovery in the aftermath, when many key players in health care and governmental institutions would have perished.

*Kenneth W T Tsang, Philip Eng, C K Liam, Young-soo Shim, Wah K Lam

University Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong SAR, China (KWTT); Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Republic of Singapore (PE); Department of Medicine, University of Malaya Medical Centre, Kuala Lumpur, Malaysia (CKL); Department of Internal Medicine, Seoul National University College of Medicine, Korea (YS, WKL)
kwttsang@hku.hk

We have no conflict of interest to declare.

1 World Health Organization. Cumulative number of confirmed human cases of avian influenza A/(H5N1) since 28 January 2004. May 4, 2005: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2005_05_04/en/index.html (accessed May 8, 2005).
2 Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med* 2005; **352:** 333–40.
3 Zeitlin GA, Maslow MJ. Avian influenza. *Curr Infect Dis Rep* 2005; **7:** 193–99.
4 Kirkbride HA, Watson J. Review of the use of neuraminidase inhibitors for prophylaxis of influenza. *Commun Dis Public Health* 2003; **6:** 123–27.
5 World Health Organization. National influenza pandemic plans. 2005: http://www.who.int/csr/disease/influenza/nationalpandemic/en/ (accessed May 8, 2005).
6 GlaxoSmithKline. Relenza datasheet. Issue number 5. June 8, 2000. Evreux, France: Galxo Wellcome Production, 2000: http://www.msds-gsk.com/uk_presc/11057406.pdf (accessed June 1, 2005).
7 Hoffmann-La Roche. Tamiflu datasheet. Core data sheet version 1.5. May, 3 2004. Basel: F Hoffmann-La Roche, 2001: http://www.medsafe.govt.nz/profs/Datasheet/t/Tamiflucapsusp.htm (accessed June 3, 2005).
8 The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet* 1998; **352:** 1877–81.
9 Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 2000; **283:** 1016–24.
10 McKimm-Breschkin JL. Management of influenza virus infections with neuraminidase inhibitors: detection, incidence, and implications of drug resistance. *Treat Respir Med* 2005; **4:** 107–16.
11 Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004; **364:** 759–65.
12 Tran TH, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med* 2004; **350:** 1179–88.
13 Imuta F, Toyoda M, Toyoda T. New application method of zanamivir with a straw. *Pediatr Int* 2003; **45:** 366–67.
14 Murphy KR, Eivindson A, Pauksens K, et al. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: a double-blind, randomized, placebo-controlled multicentre study. *Clin Drug Invest* 2000; **20:** 337–49.
15 Cass LM, Brown J, Pickford M, et al. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. *Clin Pharmacokinet* 1999; **36** (suppl 1)**:** 21–31.
16 Hill LS, Slater AL. A comparison of the performance of two modern multidose dry powder asthma inhalers. *Respir Med* 1998; **92:** 105–10.
17 Webby RJ, Webster RG. Are we ready for pandemic influenza? *Science* 2003; **302:** 1519–22.
18 Tzeng HM. Nurses' professional care obligation and their attitudes towards SARS infection control measures in Taiwan during and after the 2003 epidemic. *Nurs Ethics* 2004; **11:** 277–89.