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Confronting an influenza pandemic with inexpensive generic agents: can it be done?

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Avian influenza A H5N1 presents a serious and possibly imminent pandemic threat. In such an event, adequate supplies of affordable vaccines and antiviral agents will be unavailable to most people in the world. In view of the overwhelming need for effective alternatives, generic agents that target the host immune response or the pandemic virus should be considered. Many scientists doubt the effectiveness of these agents. Nonetheless, several studies suggest that statins improve outcomes in patients with bacteraemia and pneumonia and might be similarly effective against influenza. An experimental study has shown that the fibrate gemfibrozil, a peroxisome proliferator-activated receptor (PPAR) α agonist, reduces mortality in H2N2 influenza virus-infected mice. There is substantial molecular cross-talk between statins and PPAR agonists, and their clinical effects are additive in patients with cardiovascular diseases. Chloroquine increases endosomal pH, impairing influenza virus release into the cytosol. Statins, fibrates, and chloroquine are produced as generic medications in developing countries. They are inexpensive, could be stockpiled, and would be available on the first pandemic day. With a lack of realistic alternatives for confronting the next pandemic, research is urgently needed to determine whether these and other generic agents could mitigate the effects of what might otherwise become an unprecedented global public-health crisis.

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Introduction

It is now clear to health officials around the world that another influenza pandemic is inevitable. If it is imminent, adequate supplies of affordable vaccines will be unavailable to most people in the world.[1–3] Supplies of antiviral agents will be even more limited and growing concern about antiviral resistance will discourage further pandemic stockpiling.[4] New types of antiviral agents will not be introduced into clinical practice for many years.[5]

In view of the overwhelming need for an effective alternative to vaccines and antiviral agents, it has been suggested that anti-inflammatory and immunomodulatory agents might benefit people when the next pandemic arrives.[6] This suggestion is based in part on observations that severe infections caused by influenza A H5N1, the 1918 Spanish influenza H1N1, and seasonal influenza A viruses are characterised by increased levels of several proinflammatory cytokines and chemokines.[7–10] This response has sometimes been called a "cytokine storm".

Doubts about using anti-inflammatory and immunomodulatory agents for pandemic control

In an important clinical report, de Jong and colleagues[8] presented detailed virological and immunological findings on 18 patients with influenza A H5N1 and compared them with findings from eight individuals who had seasonal influenza. The H5N1-infected individuals had higher serum cytokine and chemokine levels, especially the 13 (72%) who died. They also had high viral loads in pharyngeal secretions. The investigators concluded: "although immunomodulatory treatment has potential benefits at this stage, the focus of clinical management should be on preventing the intense cytokine response by early diagnosis and effective treatment".[8] Unfortunately, all 18 patients sought medical care an average of 6 days after the onset of symptoms, and all but one were treated with a neuraminidase inhibitor.

Reports by Szretter[11] and Salomon[12] and their colleagues have cast doubt on the potential efficacy of treating H5N1 influenza virus infections with immunomodulatory agents. Both groups of investigators studied experimental infections in small groups of knockout mice in which the genes for individual proinflammatory cytokines and chemokines had been deleted. Szretter and co-workers[11] found that deleting interleukin 6 or macrophage inhibitory protein (MIP) 1α had no effect on highly pathogenic H5N1 disease or virus replication, whereas lack of interleukin-1-receptor signalling enhanced disease and delayed virus clearance. Lack of tumour necrosis factor (TNF) α also increased disease severity but had no effect on virus replication or outcome. The investigators commented that because of the functional redundancy of many cytokines and chemokines, deleting more than one of these genes might have had a greater (presumably more adverse) effect on the course of disease, and concluded that mice are suitable for evaluating agents that "modulate the inflammatory response induced by H5N1 viruses, either alone or in combination with antiviral therapy".[11]

Salomon and colleagues[12] also studied H5N1 infections in groups of mice in which different genes had been deleted—TNFα, TNF receptor 1, both TNF receptor 1 and TNF receptor 2, interleukin 6, and CC chemokine ligand (CCL) 2.[12] Each of these deletions failed to protect mice from death caused by a highly pathogenic H5N1 virus. The researchers concluded that their results "refute the popular paradigm that cytokine storm is the cause of death during H5N1 infection".[12] They added: "inhibiting the host cytokine response is not sufficient to reduce morbidity and lethality of the viral infection…early inhibition of viral replication is more promising than inhibition of the cytokine response in promoting host survival of H5N1 influenza virus infection".[12] Experts writing on behalf of WHO have concluded that

	Study design	Number of patients treated (pneumonia cases/controls)	Outcome	Adjusted odds ratio (95% CI)
van de Garde et al[25]	Case-control, diabetic patients	4719/15 322	Pneumonia hospital admission	0·50 (0.28–0·89)
Schlienger et al[26]	Case-control	1227/4734	Pneumonia hospital admission	0·63 (0·6–0·88)
			30-day pneumonia mortality	0·47 (0·25–0·88)
Mortensen et al[27]	Retrospective cohort	1566/7086†	30-day pneumonia mortality	0·54 (0·42–0·70)
Majumdar et al[28]	Prospective cohort	325/3090†	Hospital mortality/ICU admission (adjusted for administrative data)	0·88 (0·63–1·22)
			Hospital mortality/ICU admission (adjusted for age and propensity score)	1·10 (0·76–1·60)

ICU=intensive care unit. *None of the investigators was able to document whether patients who were treated with statins as outpatients were also treated following hospital admission for pneumonia. †Number of statin users/number of non-statin users.

Table: **Recent treatment with statins in patients hospitalised with pneumonia***

"knowledge of the mechanisms of hypercytokinaemia is insufficient to guide safe, rational immunomodulatory treatment at present".[13]

The host defence against infection involves both an inflammatory response and subsequent active resolution of inflammation.[14] Safe targeting of the host response must acknowledge its extraordinary complexity and the many positive and negative cell signalling pathways that keep its individual components in balance.[15] The reports of Szretter and Salomon and colleagues notwithstanding,[11,12] experiments done in small numbers of knockout mice are unlikely to provide an adequate basis for concluding that broadly acting anti-inflammatory and immunomodulatory agents will be of no benefit in treating H5N1 infections in mice or pandemic influenza in human beings. Moreover, several earlier studies in knockout mice suggest a different conclusion.

The acute inflammatory response to influenza virus infection is generated by interleukin 1α/β, which binds to the type 1 interleukin-1 receptor.[16] This response is counterbalanced by the interleukin-1-receptor antagonist, a naturally occurring anti-inflammatory cytokine. In studies comparing responses to influenza virus infection in interleukin-1-receptor antagonist knockout mice and normal mice, Schmitz and co-workers[16] showed that weight loss in the two groups was similar and lung virus titres in knockout mice increased only moderately, but mortality in knockout mice increased substantially. Thus, interleukin-1α/β-mediated pulmonary inflammatory changes had little effect on virus replication but enhanced survival.

An earlier study of the effects of the macrophage chemokine receptors CCR5 and CCR2 showed that in influenza virus-infected CCR5 knockout mice, lung virus titres were low yet pulmonary inflammation and mortality were increased compared with virus-infected CCR2 knockout mice.[17] By contrast, in CCR2 knockout mice, lung virus titres were greater, but pulmonary inflammation was less and mortality was lower. In another study, host responses to influenza virus infection were studied in mice deficient in either cyclooxygenase (COX) 1 or COX2.[18] COX1-deficient mice had lower inflammatory cytokine levels, less pulmonary inflammation, and higher lung viral titres, but better rates of survival than COX2-deficient mice.[18] More recently, a study of acute influenza pneumonia showed that compared with normal mice, Toll-like receptor (TLR) 3 knockout mice had reduced levels of several proinflammatory cytokines and chemokines and high pulmonary virus titres, yet mortality was unexpectedly low.[19] An extensive review of the immunopathology of influenza virus infection concluded: "Influenza mortality is not necessarily a direct function of virus burden, highlighting the role of immune-mediated pathology in this disease".[20]

Extrapolating the results of studies of individual cytokine responses in mice to human beings must be done with great caution. In patients with pneumonia, higher serum levels of several inflammatory cytokines were generally associated with greater severity of illness, but cytokine profiles among individual patients varied and could not be used to predict outcomes.[21]

Anti-inflammatory and immunomodulatory agents for pandemic control

The statin hypothesis

Interest in agents that might control the host immune response to pandemic influenza virus infection was initially focused on the group of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors known as statins.[6] Laboratory and clinical studies by cardiovascular investigators have shown that statins have pronounced anti-inflammatory and immunomodulatory (pleiotropic) effects. Several clinical studies have shown that statins decrease mortality in patients with bacterial sepsis.[6,22,23] These benefits are thought to be caused by a multiplicity of molecular effects that reflect statin modification of intracellular signalling cascades, a process that has been likened to "reducing the heat under a boiling kettle".[24]

Four observational studies of statins and pneumonia have been published (table).[25–28] In a case-control study, van de Garde and colleagues[25] reported that recent prescriptions for statins were associated with a 50% reduction in pneumonia hospital admissions in diabetic patients. In another case-control study, Schlienger and co-workers[26] showed that current prescriptions for statins (within 30 days) were associated with a 53% reduction in 30-day pneumonia mortality. In a retrospective cohort study by Mortensen and colleagues,[27] current statin use was associated with a 46% reduction in 30-day pneumonia mortality. However, Majumdar and colleagues[28] reached a different conclusion; their prospective cohort study failed to demonstrate a beneficial effect of statins and they ascribed the apparent benefits of statin treatment

seen in other studies to a "healthy user effect". Although the healthy user effect does exist and can be important, many "healthy users" in the study by Schlienger and colleagues[26] had been given statins in the past (more than 30 days before hospital admission) but were not taking them currently, yet only current users were protected.

None of these investigations was able to show whether statins given after pneumonia hospitalisation were associated with protection, unlike an earlier report showing a remarkable reduction in bacteraemia-attributable mortality with in-hospital statin treatment.[22] An observational study of hospitalised pneumonia patients is now underway to address this important question. Recently, investigators in South Korea reported preliminary results from a randomised controlled trial of statin treatment in 67 pneumonia patients admitted to intensive care units (ICUs).[29] Treatment with atorvastatin (10 mg daily) was associated with a 45·4% reduction in ICU mortality (p=0·08) and a 51·2% reduction in hospital mortality (p=0·026).

Although these studies suggest that statins are associated with reductions in mortality in patients with infections known to be associated with cytokine dysregulation,[2,3,6,22–27,29] no published reports have yet appeared that document their benefits in any experimental or human influenza virus infection.

PPAR agonists

Another approach to modifying the host response to influenza comes from a recent experimental study.[30] Mice were infected with an influenza A H2N2 virus and treatment began 4 days later with gemfibrozil, a fibrate that is a peroxisome proliferator-activated receptor (PPAR) α agonist. Mortality was significantly reduced in treated mice: 52% of control mice died compared with only 26% of those treated with gemfibrozil (hazard ratio 0·46, 95% CI 0·26–0·76; log rank test p=0·0026). The investigators did not study the effects of treatment on virus replication or dissemination. In their study, simvastatin was reported not to have been effective.

It has been known for many years that both PPARα and PPARγ agonists have anti-inflammatory and immunomodulatory activities, and several investigators have suggested that they might be used to treat acute lung injury.[31–33] One study showed that glitazones (PPARγ agonists) inhibit respiratory syncytial virus infection in human lung epithelial cells, probably by inhibiting viral gene expression and not earlier adhesion or fusion processes.[34] No studies have reported the direct antiviral effects of PPARα agonists, yet both PPARα and PPARγ agonists affect several intracellular signalling pathways that are crucial for influenza virus replication.[35,36] Moreover, statins and fibrates act synergistically to affect some of these pathways,[37,38] and many of the pleiotropic effects of statins are mediated by their effects on PPARs.[39] When statins are given in combination with PPARα or PPARγ agonists to patients with cardiovascular diseases and diabetes mellitus, their beneficial effects on important biomarkers of disease are additive.[40,41] Studies of five commonly used statins and two fibrates (gemfibrozil and fenofibrate) have shown that the potential for important adverse pharmacokinetic interactions is lower for fenofibrate/statin combinations.[42] Prolonged combination therapy with fibrates in adults is safe and well tolerated, suggesting that short-term prophylaxis or acute treatment for influenza, if clinically effective, would also be acceptable.

Thus far, clinical and epidemiological studies of pneumonia patients suggest only that statins might benefit influenza patients.[2,3,6,25–27,29] In the study by Schlienger and colleagues,[26] fibrates taken at any time had no effect on pneumonia outcomes. Moreover, none of the general changes in cell signalling induced by statins and fibrates has been documented for these agents in experimental influenza. However, it is worth noting that the severity of experimental endotoxin-induced acute lung injury is directly proportional to the duration and intensity of nuclear factor (NF) κB activity and that downregulating NFκB even after the onset of pulmonary inflammation is beneficial.[43] NFκB is known to suppress the antiviral and immunomodulatory effects of interferon in influenza virus-infected cells.[44] Both statins[24] and PPAR agonists[31–33,38] downregulate NFκB activity.

Investigators have yet to show that treating experimental H5N1 or 1918 influenza H1N1 virus infections with an anti-inflammatory or immunomodulatory agent is beneficial. Nonetheless, the finding that gemfibrozil alone significantly reduced mortality in influenza H2N2-infected mice is of great importance.[30] This result shows that the outcome of a severe influenza virus infection can be improved by modifying key steps in cell signalling with an agent that has no known antiviral activity. It provides "proof of principle" that targeting the host response without attacking the virus could be beneficial, contradicting the views of those who think it would not be useful.[8,12]

An available and affordable antiviral agent to complement statins and fibrates

Until now, influenza virologists have emphasised pandemic treatment strategies that target the virus.[5] No one would seriously argue against using effective antiviral agents, but for the foreseeable future these agents (mainly neuraminidase inhibitors) will remain expensive and in short supply. Thus, in addition to identifying one or more effective anti-inflammatory and immunomodulatory agents, identifying an effective, inexpensive, and universally available antiviral agent must be a high priority.

Chloroquine has been suggested as one such agent. This drug has well-established anti-inflammatory activity and is sometimes used to treat immune-mediated diseases such as rheumatoid arthritis.[45] Chloroquine's antiviral activity against influenza viruses was first demonstrated in the early 1980s and within the past few years it has also been

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Figure: **Generic drugs are cheap, safe, and widely available in developing countries**

shown to possess in-vitro antiviral activity against other viruses, including HIV-1 and severe acute respiratory syndrome coronavirus.[45–48] Chloroquine accumulates in the endosome where it interferes with acidification and thereby impairs viral fusion and release into the cytosol. Different influenza virus subtypes respond differently to chloroquine, with H3N2 and H1N1 viruses being more susceptible than certain H5 viruses.[48] Structural determinants on subunit 2 of the haemagglutinin molecule seem to determine the antiviral response. The in-vitro antiviral effects of chloroquine and the neuraminidase inhibitor oseltamivir have been shown to be additive.[48]

The in-vivo efficacy of chloroquine was recently tested in models of influenza A H1N1 virus infection in mice and H3N2 infection in ferrets.[49] Chloroquine treatment was not associated with clinical improvement, but virus titres in lung tissue (mice) and nasal wash specimens (ferrets) obtained later in the course of illness were reported to be lower in treated animals compared with controls. This finding suggests that an antiviral effect might have occurred but that it failed to bring about clinical improvement because cytokine dysregulation was able to proceed regardless of whether virus replication continued or was suppressed. If this is what happened, it is conceivable that limiting virus replication with chloroquine while at the same time treating the immune response with a fibrate, statin, or other promising agents might have led to clinical recovery. Support for this interpretation comes from another report on the proinflammatory and anti-inflammatory responses of influenza virus-infected mice with secondary pneumococcal pneumonia.[50] In this model, there were no differences in the outcomes of mice with or without bacteraemia or with high or low levels of bacterial growth in their lungs; all mice in all groups developed rapidly fatal illness. When mice were dually infected with influenza virus and *Streptococcus pneumoniae* and then treated with either ampicillin or clindamycin, ampicillin was more effective in clearing pneumococci from the lung, but survival was improved with clindamycin.[51] It seems that factors determining survival involved something more than killing the infecting pneumococci. In other studies of mice infected with influenza viruses alone, other macrolides have been shown to inhibit nitric oxide production, increase interleukin 12 in bronchoalveolar fluid, reduce both virus replication and pulmonary inflammation, and improve survival.[52,53]

Other inexpensive and widely distributed agents should also be considered for their potential as antivirals against influenza.[4] For example, resveratrol, a polyphenol with antioxidant properties that is found in red wine, has been shown to inhibit replication of influenza viruses in vitro and reduce mortality and virus titres in the lungs of infected mice.[54] Its antiviral activity does not depend on its antioxidant properties; instead, resveratrol blocks the translocation of viral ribonucleoprotein complexes from the nucleus to the cytoplasm during the late stage of infection, probably by interfering with the activity of several protein kinases. Resveratrol also targets TLR cell signalling pathways and interferes with the related upregulation of several proinflammatory cytokines and chemokines that contribute to the inflammatory host response.[55] These important findings appear to have attracted no attention from influenza scientists.

There are many examples of virus infections in which the virus replicates to similar levels in related species, killing one but causing no disease in the other—for example, infection with simian immunodeficiency virus is fatal to macaques, but in sooty mangabeys infection causes no disease, despite high levels of virus replication.[56] In the two species, it is the host immune response that determines outcome.[56] Moreover, infectious diseases such as tuberculosis and bacterial sepsis respond better to treatment with two or more agents than to only one, with some agents targeting the pathogen while others treat the host. Can the same approach be used for pandemic treatment and prophylaxis? Is an effective "bottom up" approach using one or more widely available generic agents a realistic possibility?[2–3,6]

The global public-health importance of generic agents

One of the avian influenza A H5N1 viruses currently causing sporadic human disease might become efficiently transmissible between human beings and lead to a pandemic. Although the probability that this will occur is unknown,[7,13] health officials and influenza experts, whether through unwillingness or inability to "envision the worst",[2,57] have remained silent on the potential enormity of an H5N1 pandemic: it could conceivably cause the deaths of hundreds of millions of people worldwide. The theoretical possibility that this could happen was shown experimentally more than 30 years ago.[58] Thus, the implications of being able to

successfully confront the next pandemic with one or more widely available generic antiviral and immunomodulatory agents are immense.

A major reason for the initial interest in using statins for pandemic treatment and prophylaxis is the universal affordability and accessibility of one of these agents. Generic simvastatin is now produced by almost 100 companies, over half of which are located in China and India.[3] In developing countries, a 5-day course of treatment would probably cost US$0·50. Gemfibrozil and fenofibrate (a clinically more acceptable PPARα agonist) are also produced as generic agents by at least 20 companies, many of them located in developing countries. In Canada and the USA, a 5-day treatment course with a fibrate would cost less than $2·00 and in developing countries probably much less. Equally important, chloroquine and hydroxychloroquine are generically produced, very inexpensive, and could be made available worldwide.

For reasons of global public health it is crucially important for investigators to undertake experimental studies to determine whether these or other generic agents (or several of them in combination) could be effective in treating H5N1 and other potentially pandemic influenza virus infections. Individual agents might act directly on the virus itself or stabilise the cardiopulmonary response of the host to infection, or both.[6] The primary goal of the research, however, should be to identify specific agents that can be used to manage a pandemic rather than to simply explain the molecular mechanisms by which they work. The research must include the human pharmacokinetics of each agent, potential dosing regimens for acute treatment and prophylaxis, important drug–drug interactions, and safety, especially in children and pregnant women. Any agent found to be effective could be stockpiled and would be available and affordable to people in developing countries on the first pandemic day (figure). The same will never be said for pandemic vaccines and current antiviral agents. Moreover, no matter when the next pandemic virus emerges and no matter how severe the pandemic might be, this research will directly inform the prevention and control of seasonal influenza.

Conclusions

There is no guarantee that generic agents will be useful for pandemic treatment and prophylaxis. Nonetheless, if we believe the next pandemic could be imminent, we have two alternatives: we can either do this research before the pandemic arrives and perhaps show that generic agents will not be useful or we can do it after the pandemic has passed and perhaps discover that millions of people could have been saved. We can no longer avoid this choice.

More than 85% of the world's population will not have meaningful access to pandemic vaccines or antiviral agents.[1–3] Consequently, health officials, especially those in countries without these treatments, must consider entirely new approaches to confronting a pandemic. They must support investigators willing to study any existing agent that has promising antiviral or anti-inflammatory and immunomodulatory activities. These agents must be identified from among the large number that are already licensed,[59] produced as generics by companies in developing countries, and sold at prices that are affordable to people everywhere.

The reports reviewed here deserve the attention of all investigators who are working on ways to confront the next pandemic. They emphasise once again that "given their low cost, safety, and worldwide availability, generic (agents) could become crucially important for confronting the next pandemic. They could greatly reduce the disparity that will otherwise separate developed and developing countries".[6] Generic agents could become the only measures to alter the course of what otherwise might become an unprecedented global health crisis. For this reason, the research agenda suggested by these reports demands the immediate attention of laboratory and clinical investigators, health officials, and political leaders throughout the world. We simply cannot afford not to undertake this work.

Conflicts of interest

I have received speaker's fees from Sanofi Pasteur and consultation fees from Crucell, Dynavax, Merck, and Sanofi Pasteur.

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References

1 Fedson DS. Vaccine development for an imminent pandemic. Why we should worry, what we should do. *Hum Vaccin* 2006; **2:** 38–42.
2 Fedson DS, Dunnill P. New approaches to confronting an imminent influenza pandemic. *Perm J* 2007; **11:** 63–69.
3 Fedson DS, Dunnill P. From scarcity to abundance; pandemic vaccines and other agents for "have not" countries. *J Public Health Policy* 2007; **28:** 322–40.
4 ECDC. Resistance to oseltamivir (Tamiflu) found in some European influenza virus samples. Updated March 26, 2008. Stockholm: European Centre for Disease Prevention and Control. http://ecdc.europa.eu/Health_topics/influenza/antivirals.html (accessed March 31, 2008).
5 Basler CF. Influenza viruses: basic biology and potential drug targets. *Infect Disord Drug Targets* 2007; **7:** 282–93.
6 Fedson D. Pandemic influenza: a potential role for statins in treatment and prophylaxis. *Clin Infect Dis* 2006; **43:** 199–205.
7 Peiris JS, de Jong MD, Guan Y. Avian influenza virus A (H5N1): a threat to human health. *Crit Microbiol Rev* 2007; **20:** 243–67.
8 de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* 2006; **12:** 1203–07.
9 Kobasa D, Jones SM, Shinya K, et al. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature* 2007; **445:** 319–23.
10 Lee N, Wong CK, Chan PK, et al. Hypercytokinemia and hyperactivation of phospho-p38 mitogen-activated protein kinase in severe human influenza A virus infection. *Clin Infect Dis* 2007; **45:** 723–31.
11 Szretter KJ, Gangappa S, Lu X, et al. Role of host cytokine responses in the pathogenesis of avian H5N1 influenza viruses in mice. *J Virol* 2007; **81:** 2736–44.
12 Salomon R, Hoffmann E, Webster R. Inhibition of the cytokine response does not protect against lethal H5N1 influenza infection. *Proc Natl Acad Sci USA* 2007; **104:** 12479–81.
13 Writing Committee of the Second World Health Organization Consultation on clinical aspects of human infection with avian influenza A (H5N1) virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008; **358:** 261–73.

14 Serhan CN, Brain SD, Buckley CD, et al. Resolution of inflammation: state of the art, definitions and terms. *FASEB J* 2007; **21:** 325–32.

15 Brown KL, Cosseau C, Gardy JL, Hancock RE. Complexities of targeting innate immunity to treat infection. *Trends Immunol* 2007; **28:** 260–66.

16 Schmitz N, Kurrer M, Bachmann MF, Kopf M. Interleukin-1 is responsible for acute lung immunopathology but increases survival of respiratory influenza virus infection. *J Virol* 2005; **79:** 6441–48.

17 Dawson TC, Beck MA, Kuziel WA, Henderson F, Maeda N. Contrasting effects of CCR5 and CCR2 deficiency in the pulmonary inflammatory response to influenza A virus. *Am J Pathol* 2000; **156:** 1951–59.

18 Carey MA, Bradbury JA, Seubert JM, Langenbach R, Zeldin DC, Germolec DR. Contrasting effects of cyclooxygenase-1 (COX-1) and COX-2 deficiency on the host response to influenza A viral infection. *J Immunol* 2005; **175:** 6878–84.

19 Le Goffic R, Balloy V, Lagranderie M, et al. Detrimental contribution of the Toll-like receptor (TLR)3 to influenza A virus-induced acute pneumonia. *PLoS Pathog* 2006; **2:** e53.

20 La Gruta NL, Kedzierska K, Stambas J, Doherty PC. A question of self-preservation: immunopathology in influenza virus infection. *Immunol Cell Biol* 2007; **85:** 85–92.

21 Kellum JA, Kong L, Fink MP, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; **167:** 1655–63.

22 Kruger P, Fitzsimmons K, Cook D, Jones M, Nimmo G. Statin therapy is associated with few deaths in patients with bacteremia. *Intensive Care Med* 2006; **32:** 75–79.

23 Almog Y, Novack V, Eisinger M, Porath A, Novack L, Glutz H. The effect of statin therapy on infection-related mortality in patients with atherosclerotic disease. *Crit Care Med* 2007; **35:** 372–78.

24 Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins and sepsis: multiple modifications at multiple levels. *Lancet Infect Dis* 2007; **7:** 358–68.

25 van de Garde EM, Hak E, Souverein PC, Hoes AW, van den Bosch JM, Leufkens HG. Statin therapy and reduced risk of pneumonia in patients with diabetes. *Thorax* 2006; **61:** 957–61.

26 Schlienger RG, Fedson DS, Jick SS, Jick H, Meier CR. Statins and risk of pneumonia: a population-based, nested case-control study. *Pharmacotherapy* 2006; **27:** 525–32.

27 Mortensen EM, Pugh MJ, Copeland A, et al. Impact of statins and ACE inhibitors on mortality for subjects hospitalized with pneumonia. *Eur Respir J* 2008; **32:** 611–17.

28 Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ* 2006; **333:** 999–1004.

29 Choi HS, Park MJ, Kang HM, Kim IH, Choi CW, You JH. Statin use and mortality in sepsis due to pneumonia. *Crit Care Med* 2007; **35** (suppl 12): A15.

30 Budd A, Alleva L, Alsharifi M, et al. Increased survival after gemfibrozil treatment of severe mouse influenza. *Antimicrob Agents Chemother* 2007; **51:** 2965–68.

31 Cuzzocrea S. Peroxisome proliferator-activated receptors and acute lung injury. *Curr Opin Pharmacol* 2006; **6:** 263–70.

32 Becker J, Delayre-Orthez C, Froissard N, Pons F. Regulation of inflammation by PPARs: a future approach to treat lung inflammatory diseases? *Fundam Clin Pharmacol* 2006; **20:** 429–47.

33 Di Paola R, Cuzzocrea S. Peroxisome proliferator-activated receptors and acute lung injury. *PPAR Res* 2007; **2007:** 63745.

34 Arnold R, Konig W. Peroxisome proliferator-activated receptor-gamma agonists inhibit the replication of respiratory syncytial (RSV) in human lung epithelial cells. *Virology* 2006; **350:** 335–46.

35 Gardner OS, Dewar BJ, Graves LM. Activation of mitogen-activated protein kinases by peroxisome proliferators-activated receptor ligands: an example of nongenomic signaling. *Mol Pharmacol* 2005; **68:** 933–41.

36 Ludwig S, Pleschaka S, Planz O, Wolff T. Ringing the alarm bells: signalling and apoptosis in influenza virus infected cells. *Cell Microbiol* 2006; **8:** 375–86.

37 Martin G, Duez H, Blanquart C, et al. Statin-induced inhibition of the Rho-signaling pathway activates PPARalpha and induces HDL apoA-I. *J Clin Invest* 2001; **107:** 1423–32.

38 Inoue I, Itoh F, Aoyagi S, et al. Fibrate and statin synergistically increase the transcriptional activities of PPARalpha/RXRalpha and decrease the transactivation of NFkappaB. *Biochem Biophys Res Commun* 2002; **290:** 131–39.

39 Paumelle R, Staels B. Peroxisome proliferator-activated receptors mediate pleiotropic actions of statins. *Circ Res* 2007; **100:** 1394–95.

40 Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol* 2005; **95:** 462–68.

41 Hanefeld M, Marx N, Pfutzner A, et al. Anti-inflammatory effects of pioglitazone and/or simvastatin in high cardiovascular risk patients with elevated high sensitivity C-reactive protein: the PIOSTAT Study. *J Am Coll Cardiol* 2007; **49:** 290–97.

42 Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. *Expert Opin Drug Saf* 2006; **5:** 145–56.

43 Everhart MB, Han W, Sherrill TP, et al. Duration and intensity of NF-κB activity determine the severity of endotoxin-induced acute lung injury. *J Immunol* 2006; **176:** 4995–5005.

44 Wei L, Sandbulte MR, Thomas PG, Webby RJ, Homayouni R, Pfeffer LM. NFkappaB negatively regulates interferon-induced gene expressions and anti-influenza activity. *J Biol Chem* 2006; **281:** 11678–84.

45 Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 2003; **3:** 722–27.

46 Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. *Lancet Infect Dis* 2006; **6:** 67–69.

47 Ooi EE, Chew JS, Loh JP, Chua RC. In vitro inhibition of human influenza A virus replication by chloroquine. *Virol J* 2006; **3:** 39.

48 Di Trani L, Savarino A, Campitelli L, et al. Different pH requirments are associated with divergent inhibitory effects of chloroquine on human and avian influenza A viruses. *Virol J* 2007; **4:** 39.

49 Vigerust DJ, McCullers JA. Effectiveness of chloroquine against influenza. *Influenza Other Respir Virus* 2008; **1:** 189–92.

50 Smith MW, Schmidt JE, Rehig JE, Orihuela CJ, McCullers JA. Induction of pro- and anti-inflammatory molecules in a mouse model of pneumococcal pneumonia after influenza. *Comp Med* 2007; **57:** 82–89.

51 Karlstrom A, McCullers JA. Outcomes from secondary pneumococcal pneumonia following influenza are improved by treatment with a protein synthesis inhibitor. 47th Intersociety Conference on Antimicrobial Agents and Chemotherapy; Chicago, USA; Sept 17–20, 2007. Abstract B-834.

52 Sato K, Suga M, Akaike T, et al. Therapeutic effect of erythromycin on influenza virus-induced lung injury in mice. *Am J Respir Crit Care Med* 1998; **157:** 853–57.

53 Tsurita M, Kurokawa M, Imakita M, Fukuda Y, Watanabe Y, Shiraki K. Early augmentation of interleukin (IL)-12 level in the airway of mice administered orally with clarithromycin or intranasally with IL-12 results in alleviation of influenza infection. *J Pharmacol Exp Ther* 2001; **298:** 362–68.

54 Palamara AT, Nencioni L, Aquilano K, et al. Inhibition of influenza A virus replication by resveratrol. *J Infect Dis* 2005; **191:** 1719–29.

55 Youn HS, Lee JY, Fitzgerald KA, Young HA, Akira S, Hwang DH. Specific inhibition of MyD88-independent signaling pathways of TLR3 and TLR4 by resveratrol: molecular targets are TBK1 and RIP1 in TRIF complex. *J Immunol* 2005; **175:** 3339–46.

56 Silvestri G, Fedanov A, Germon S, et al. Divergent host responses during primary simian immunodeficiency virus SIVsm infection of natural sooty mangabey and nonnatural rhesus macaque hosts. *J Virol* 2005; **29:** 4043–54.

57 Cerulo KA. Never saw it coming: cultural challenges to envisioning the worst. Chicago: University of Chicago Press, 2006.

58 Webster RG, Campbell CH. Studies on the origin of pandemic influenza. IV. Selection and transmission of "new" influenza viruses in vivo. *Virology* 1974; **62:** 404–13.

59 Chong CR, Sullivan DJ. New uses for old drugs. *Nature* 2007; **448:** 645–46.