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Review

Treating influenza with statins and other immunomodulatory agents

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ABSTRACT

Statins not only reduce levels of LDL-cholesterol, they counteract the inflammatory changes associated with acute coronary syndrome and improve survival. Similarly, in patients hospitalized with laboratory-confirmed seasonal influenza, statin treatment is associated with a 41% reduction in 30-day mortality.

Most patients of any age who are at increased risk of influenza mortality have chronic low-grade inflammation characteristic of metabolic syndrome. Moreover, differences in the immune responses of children and adults seem responsible for the low mortality in children and high mortality in adults seen in the 1918 influenza pandemic and in other acute infectious and non-infectious conditions. These differences probably reflect human evolutionary development. Thus the host response to influenza seems to be the major determinant of outcome.

Outpatient statins are associated with reductions in hospitalizations and deaths due to sepsis and pneumonia. Inpatient statins are also associated with reductions in short-term pneumonia mortality. Other immunomodulatory agents – ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), PPARγ and PPARα agonists (glitazones and fibrates) and AMPK agonists (metformin) – also reduce mortality in patients with pneumonia (ACEIs, ARBs) or in mouse models of influenza (PPAR and AMPK agonists). In experimental studies, treatment has not increased virus replication. Thus effective management of influenza may not always require targeting the virus with vaccines or antiviral agents.

Clinical investigators, not systems biologists, have been the first to suggest that immunomodulatory agents might be used to treat influenza patients, but randomized controlled trials will be needed to provide convincing evidence that they work. To guide the choice of which agent(s) to study, we need new types of laboratory research in animal models and clinical and epidemiological research in patients with critical illness. These studies will have crucial implications for global public health. During the 2009 H1N1 influenza pandemic, timely and affordable supplies of vaccines and antiviral agents were unavailable to more than 90% of the world's people. In contrast, statins and other immunomodulatory agents are currently produced as inexpensive generics, global supplies are huge, and they would be available to treat patients in any country with a basic health care system on the first pandemic day. Treatment with statins and other immunomodulatory agents represents a new approach to reducing mortality caused by seasonal and pandemic influenza. This article forms part of a symposium in *Antiviral Research* on "Treatment of influenza: targeting the virus or the host".

Contents

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1. Introduction

The re-emergence of the influenza A (H5N1) avian influenza virus in 2003 led to a recognition that it might be difficult to confront an H5N1 pandemic with a conventional approach that relies only on vaccines and antiviral agents. At an Institute of Medicine meeting in 2004, I suggested that treating patients with statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) might reduce pandemic mortality (Fedson, 2005, 2006). Eight years later, Vandermeer et al. reported the results of a prospective observational cohort study of statin treatment conducted in the US during the 2007–2008 seasonal influenza epidemic (Vandermeer et al., 2012; Walsh, 2012). They studied 3043 older adults who had been hospitalized with laboratory-confirmed influenza. In a multivariable logistic regression analysis that adjusted for demographic factors, high-risk conditions, previous influenza vaccination and antiviral treatment, 1013 (33.3%) statin-treated patients had a 41% reduction in mortality within 30 days of a positive influenza test (adjusted odds ratio [OR] 0.59; 95% confidence interval [CI] 0.38–0.92).

In this article, I review the background for the idea of treating influenza patients with statins and other immunomodulatory agents. I start with an account of its genesis in the experience of statin treatment of patients with acute coronary syndrome. I then present several new thoughts on risk factors responsible for influenza mortality and review clinical and epidemiological studies that support the treatment of influenza with statins and other agents. Next, I review what has been learned from animal models of immunomodulatory treatment and discuss how this fits in with views on influenza pathogenesis. Finally, I update a previously published research agenda for immunomodulatory treatment and outline the importance of this research for global public health. I have discussed several although not all of these issues in earlier publications, and readers may wish to consult these articles for more detailed information (Fedson, 2008, 2009a, 2009b, 2009c, 2011, 2012; Fedson and Dunnill, 2007; Fedson and Opal 2012, 2013).

2. Acute coronary syndrome, statins, and their relevance to influenza

In acute coronary syndrome (ACS, including acute myocardial infarction), acute inflammatory changes are superimposed on chronic underlying inflammation and pathological changes in the coronary circulation. The benefits of statins for patients with ACS occur primarily as a result of their pleiotropic effects on acute inflammation (Zhou and Liao, 2010; Mills et al., 2011). Among their many effects on cell signaling, statins cause a rapid reduction in circulating levels of pro-inflammatory cytokines (Link et al., 2006; Hua et al., 2008) and directly improve coronary endothelial function (Wassmann et al., 2003). Observational studies show that inpatient statins significantly reduce early ACS mortality, and this effect can be seen within the first few days (Fig. 1) (Ferrieres et al., 2005; Fonarow et al., 2005; Lenderink et al., 2006). Sudden withdrawal of statin treatment is quickly followed by a rebound in pro-inflammatory cytokine levels (Sposito et al., 2009) and an increase in ACS mortality (Fonarow et al., 2005).

These observational findings have not been replicated in a randomized controlled trial, probably because cardiologists accept the findings of observational studies and routinely give statins to their hospitalized ACS patients. However, in patients with coronary artery disease who undergo percutaneous coronary interventions (PCI; e.g., coronary angiography, coronary thrombolysis, stent placement), both observational studies (Liakopoulos et al., 2008; Norris and Anderson, 2012) and randomized controlled trials (Schoueten et al., 2009; Patti et al., 2011) show that statins are

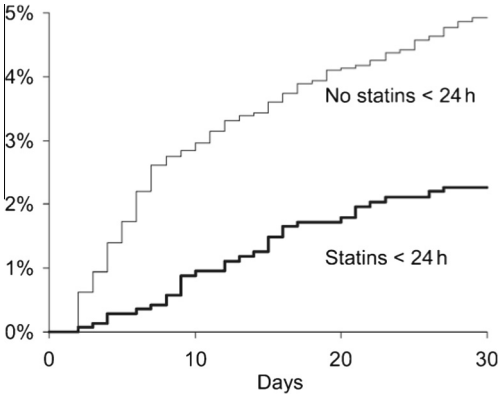

Fig. 1. Among 8197 consecutive patients who survived the first 24 h of hospitalization for acute coronary syndrome (ACS), 1426 (17.4%) were given statins for the first time and 6771 (82.6%) were not. Hazard ratios (HR) for mortality were determined in a multivariate analysis that adjusted for propensity score for statin treatment within the first 24 h, age, vital signs, Killip class, high-risk medical conditions, history of percutaneous coronary intervention and treatment with several drugs within 24 h, including aspirin, beta blockers and ACE inhibitors. For statin users, the adjusted HR for 7-day all-cause mortality was 0.34 (95% CI 0.15–0.79). For ST-elevation ACS mortality (the most severe form of ACS), the 7-day adjusted HR was 0.17 (95% CI 0.04–0.70) and for 30-day mortality it was 0.49 (0.25–0.05) (Lenderink et al., 2006; reproduced with permission).

associated with a significantly reduced occurrence of post-PCI major adverse coronary events.

More than a decade ago, epidemiologists demonstrated that influenza and other acute respiratory infections were associated with an increased incidence of acute coronary syndrome (reviewed in Corrales-Medina et al., 2010, 2012, 2013; Warren-Gash et al., 2009; Mandal et al., 2011), and more recent studies have extended this association to stroke (Elkind et al., 2011) and venous thromboembolic disease (Schmidt et al., 2012). Also during this period, experimental and clinical studies showed that influenza is accompanied by elevations in pro-inflammatory cytokines (Hayden et al., 1998; Kaiser et al., 2001). Thus, in 2004, it seemed reasonable to assume that if statin treatment was associated with improved outcomes in one disease characterized by elevated pro-inflammatory cytokines (ACS), similar improvement might be seen in another disease (influenza) also associated with hypercytokinemia (Fedson, 2005, 2006).

When I first published this hypothesis, it was based solely on an extension of the phenotypic benefits of statin treatment in one syndrome to another. At the time, this idea was supported by experimental studies showing that statin treatment improved outcomes in mouse models of sepsis (Merx et al., 2005) and acute lung injury (Jacobson et al., 2005).

3. Risk factors for influenza mortality

3.1. Metabolic syndrome

The recent 2009 H1N1 pandemic showed once again that severe or fatal influenza in people of any age largely affects those with specific underlying high-risk conditions (Van Kerkhove et al., 2011). These conditions share one feature in common: chronic low-grade inflammation that is associated with what cardiovascular scientists call metabolic syndrome (Cornier et al., 2008; Robinson et al., 2011). Metabolic syndrome is found in patients with cardiopulmonary diseases (Kupeli et al., 2010; Minas et al., 2011), diabetes mellitus (Romeo et al., 2012), hepatic and renal diseases (Stepanova et al., 2010; Slee, 2012); obesity (Lumeng and Saltiel, 2011); and asthma (Agrawal et al., 2011). In pregnancy, a certain degree of immunosuppression increases susceptibility to secondary infection (Rowe et al., 2011; Pazos et al., 2012), but pregnant women also have elements of metabolic syndrome (Baliutaviciene et al., 2012). Acute or chronic stress can also activate low-grade inflammatory responses (Fleshner, 2013). In each of these conditions, the "innate immune rheostat" is set at a different and perhaps more precarious level (Hussell and Cavanagh, 2009). It is widely known that statins have broad anti-inflammatory effects in persons with metabolic syndrome (Devaraj et al., 2006).

3.2. Secondary bacterial pneumonia in the 1918 influenza pandemic

In the 1918 influenza pandemic, there was remarkably high mortality in younger adults, but lower mortality in children and older adults (the W-shaped mortality curve; Fig. 2) (Nuzum et al., 1919; Ahmed et al., 2007; Viboud et al., 2013). Older adults had lower mortality because of persisting immunity following influenza in earlier years, but the cause of the high mortality in young adults has remained a mystery (Ahmed et al., 2007; Taubenberger et al., 2012). Increased mortality was also seen in young adults in the recent 2009 influenza pandemic (Fowlkes et al., 2011; Myles et al., 2012), and W-shaped morbidity curves have been documented in seasonal epidemic years (Georgantopoulos et al., 2009). (The age separating children from adults varies from study to study. It was not specified in the reviews of Ahmed et al., 2007 and Taubenberger et al., 2012, but it was <18 years of age in Fowlkes et al., 2011 and Viboud et al., 2013; <16 years of age in Myles et al., 2012; and <15 years of age in Nuzum et al., 1919 and Georgantopoulos et al., 2009).

Some investigators believe that secondary bacterial pneumonia explains the increased mortality seen among young adults in 1918 (Brundage and Shanks, 2008; Morens et al., 2008; Battinger and Standiford, 2010; van der Slujs et al., 2010; Morens and Taubenberger, 2012; Shanks and Brundage, 2012). Careful studies of the recent 2009 H1N1 pandemic, however, show that secondary bacterial pneumonia was seen in only a minority of patients with critical illness (Fowlkes et al., 2011; Rice et al., 2012). In my view, secondary bacterial pneumonia is not a satisfactory explanation for young adult mortality in 1918 (reviewed in Fedson, 2009c). As shown in Fig. 2, children were infected more frequently with the same virus that killed young adults, yet their mortality rate was much lower. Children were also likely to have had high rates of nasopharyngeal colonization with the same bacteria that were associated with pneumonia deaths in young adults, yet few children died. A more likely explanation is that young adults died *with* bacterial pneumonia, but not necessarily *because of* it (Fedson, 2009c). In other words, influenza induced changes in the host

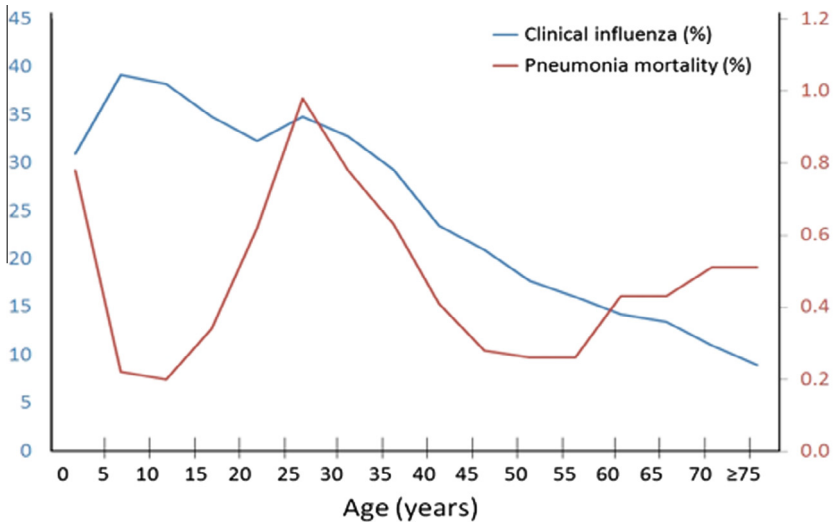

Fig. 2. The W-shaped mortality curve seen in the 1918 influenza pandemic. The curves for clinical illness and pneumonia mortality are different. Children were infected with the pandemic virus more frequently than young adults, but their pneumonia mortality rates were much lower (adapted from Fig. 5 in Brundage and Shanks, 2008; figure prepared by Nicholas Fedson).

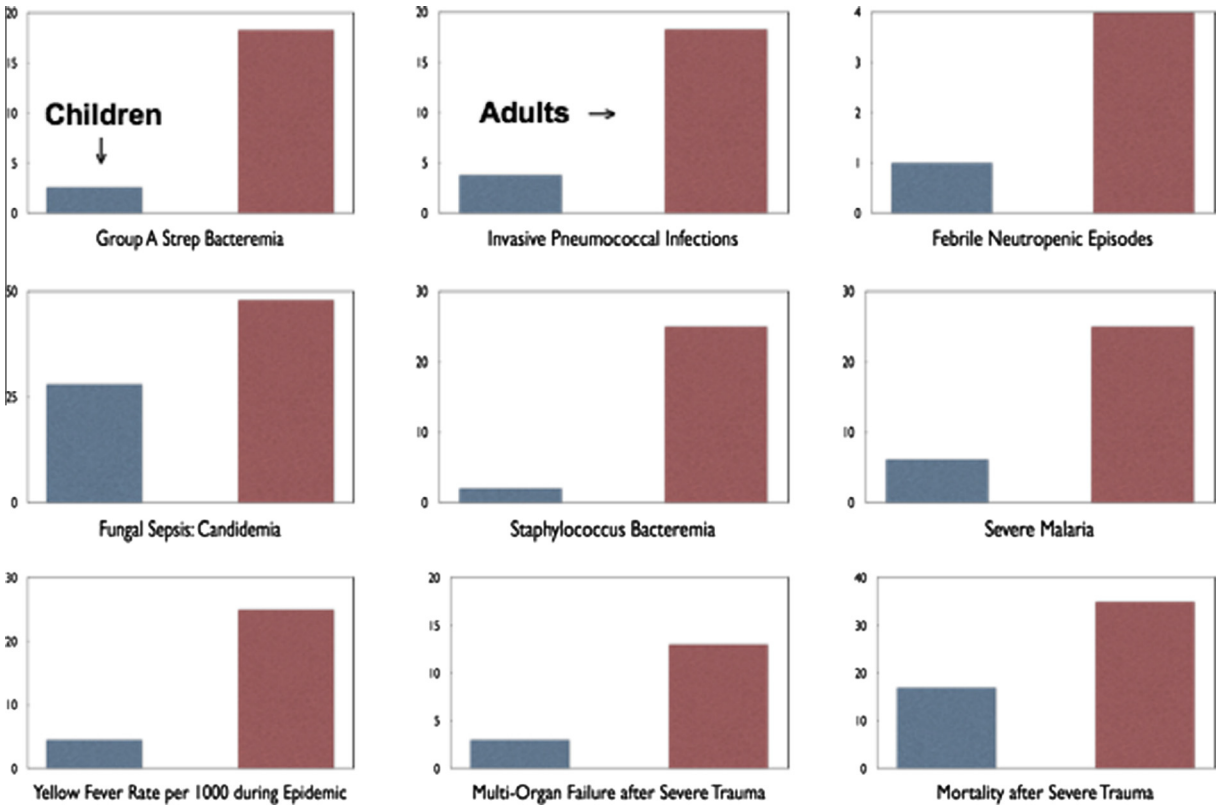

Fig. 3. Comparison of mortality rates (%) in children and adults for several infectious and non infectious diseases. See Section 3.3 in the text for details. The figure was prepared by L. Kobzik and published with permission.

response (innate and adaptive immunity) of young adults but not children, and these changes then set the stage for the secondary bacterial pneumonia that was seen in the young adults who died.

3.3. Children tolerate infectious and non infectious conditions better than adults

Lower mortality in children compared with adults is not unique to influenza. Ahmed et al. noted a similar mortality pattern for first infections with mumps, varicella zoster, polio, Epstein Barr, and hepatitis E viruses and for tuberculosis in 1918 and for SARS in 2003 (Ahmed et al., 2007). Children also have lower mortality rates than adults in Group A streptococcus bacteremia (Megged et al., 2006), invasive pneumococcal disease (Rahav et al., 1997), febrile neutropenia (Hann et al., 1997), candida fungemia (Moran et al., 2009; Pappas et al., 2003; Zaoutis et al., 2005), *Staphylococcus aureus* bacteremia (Denniston and Riordan, 2006; Laupland et al., 2008), acute lung injury seen in severe malaria (Clark et al., 2008; Dondorp et al., 2008; Randall et al., 2010), yellow fever (Thonnon et al., 1998), and multi-organ failure in trauma (Calkins et al., 2002) and severe burn injury (Finnerty et al., 2008) (Fig. 3). The same mortality difference has been documented in sickle cell chest syndrome (Johnson, 2005; Vichinsky et al., 1997, 2000) and even hemorrhagic smallpox (Downie et al., 1969). Thus, across a broad range of infectious and non-infectious conditions, mortality rates for children are lower than those of adults. The dividing line between the two occurs during the second decade of life, at about the time of puberty (Ahmed et al., 2007; Fedson, 2009c; Erkoreka, 2010).

3.4. The evolutionary origin of the mortality difference between children and adults

Surprisingly, immunologists and other investigators have rarely looked for explanations of the difference in pre- and post-pubertal mortality in animal models of sepsis (Bodas et al., 2010) and influenza (Huang et al., 2012). Recently, however, the mortality rate of PR8-infected C57BL/6 mice was shown to be much lower in the period immediately before puberty compared with the period after puberty (Suber and Kobzik, 2013). When mice were either castrated or ovariectomized to delay the onset of puberty, the low mortality rate was maintained, but when they were treated with estrogen, the mortality rate returned to the level seen in control post-pubertal mice. This new model challenges conventional ideas about influenza mortality, and it should allow virologists to undertake experiments that discriminate between host-related and virus-related factors that determine influenza-related survival and death.

Evolutionary biologists have shown that the annual probability of death declines steeply in the first few months after birth and reaches its nadir at about the time of puberty (Fig. 4) (Burger et al., 2012). It then rises steeply into the third decade of life, after which the rise is more gradual throughout the rest of life. There is no ready explanation for why the annual probability of death increases so abruptly during the second decade of life, but this is a time when the pre-pubertal focus of energy metabolism on growth ceases and reproduction becomes of primary importance.

The studies I have reviewed in this section show that different high-risk conditions share common metabolic features, that secondary bacterial pneumonia is not a satisfactory explanation for the high mortality seen in young adults in the 1918 pandemic, that differences in mortality rates of children and adults can be found across a broad range of infectious and non infectious conditions, and that these mortality differences probably have a common origin in human evolutionary development. Taken together, the findings point to host factors as the predominant determinants of outcome in influenza virus infection.

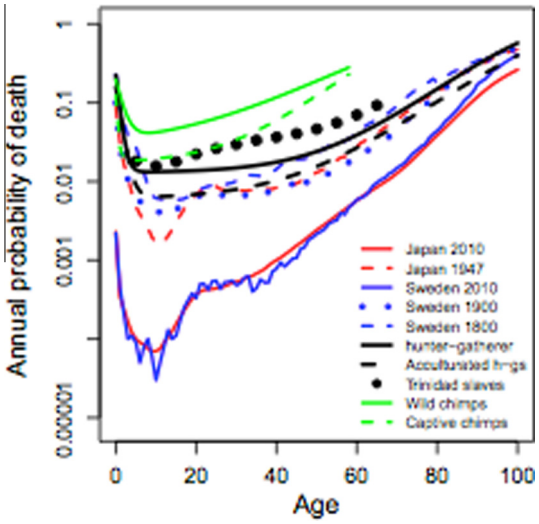

Fig. 4. Annual probability of death for several human populations and wild and captive chimpanzees. The hunter gather curve approximates the typical human profile over almost all of evolutionary time. The curves for Japan in 1947 and Japan and Sweden in 2010 demonstrate the steep rise in the modern mortality profile during the second decade of life (Burger et al., 2012; reproduced with permission).

4. Clinical studies of statin treatment of pneumonia and influenza

In my earlier articles on immunomodulatory treatment of human influenza, I focused largely on the use of statins because a large number of observational studies had documented their effects on hospitalization and mortality in patients with pneumonia. (Statins have been shown to affect outcomes in patients with sepsis and other non pulmonary forms of critical illness, but I will not review these studies here.) Although several other agents have immunomodulatory potential, the numbers of treated patients have been much smaller, and for most of these agents, no clinical studies in patients with pneumonia and influenza have been reported.

Just as statins have many effects in patients with ACS, their effects in acute lung injury are also pleotropic (reviewed in Singla and Jacobson, 2013). Space does not permit a full discussion of the probable mechanisms underlying statin effects in influenza. However, I have summarized several cell signaling pathways that might be targeted by treatment with statins and other immunomodulatory agents (Table 1).

4.1. Statins and pneumonia

A substantial number of observational studies have evaluated the effectiveness of outpatient statins in reducing rates of hospital admission and death in patients with community-acquired pneumonia (e.g., O'Neal et al., 2011; Vinogradova et al., 2011), and meta-analyses of these studies uniformly show protection (Fig. 5) (van den Hoek et al., 2011; Chalmers et al., 2012; Chopra et al., 2012; Kwok et al., 2012). A good example is a recent observational study from Denmark (Nielsen et al., 2012). (This study was not included in the earlier meta-analysis shown in Fig 5.) The Danish study reported on 70,953 adults hospitalized with pneumonia during the 1997–2009 period, among whom 10.2% had filled at least one prescription for a statin within 125 days of hospitalization. Each case was matched with ten population controls. In a highly detailed analysis that controlled for co-morbid illness, other medications and several variables that reflected frailty and health awareness, outpatient statin users had a 20% reduction in pneumonia hospitalization (adjusted OR 0.80; 95% CI 0.77–0.83), and a 27% reduction in 30-day mortality (adjusted hazard ratio [HR] 0.73; 95% CI 0.67–0.79). Although the investigators did not study pneumonia hospitalizations during influenza seasons, in a supplementary analysis for the period 2001–2009, they controlled for current seasonal influenza vaccination. During this period, current outpatient statin use was associated with a 22% reduction in pneumonia hospitalizations (adjusted OR 0.78; 95% CI 0.72–0.85) and a 24% reduction in 30-day mortality (adjusted OR 0.76; 95% CI 0.65–0.88) (Nielsen et al., 2012).

Three observational studies have reported on the effectiveness of inpatient statin treatment in patients hospitalized with pneumonia (Table 2) (Yende et al., 2011; Mortensen et al., 2012; Rothberg et al., 2012). These studies provide evidence that inpatient statin treatment is associated with a reduction in mortality in pneumonia patients. However, one or more of these studies have limitations, including lack of information on (1) statin treatment before hospital admission, (2) whether outpatient statins were discontinued at the time of hospital admission, (3) the timing and duration of inpatient statin treatment and (4) the possible confounding effects of previous influenza and pneumococcal vaccinations.

Table 1
Treating influenza with statins and other immunomodulatory agents: cell signaling pathways that might be targeted by treatment.

Up regulate HO-1[a] and decrease TLR signaling by PAMPs and DAMPs
Down regulate NF-kappaB and pro-inflammatory cytokines (e.g., TNFα, IL-1, IL-6)
Up regulate anti-inflammatory cytokines (IL-10)
Up regulate pro-resolution factors (lipoxin A4)
Down regulate HMGB1/RAGE and late mediators of inflammation
Up regulate adipokines (adiponectin) that decrease inflammation
Up regulate eNOS, down regulate iNOS, restore iNOS/eNOS balance and stabilize cardiovascular function
Decrease formation of reactive oxygen species and reduce oxidative stress
Decrease tissue factor and its associated pro-thrombotic state
Attenuate the C5a-C5aR-related increase in vascular endothelial permeability
Stabilize the actin cytoskeleton and adherens and tight junctions in endothelial cells, increase pulmonary barrier integrity and decrease vascular leak
Attenuate acute influenza-associated pulmonary hypertension
Restore the balance between Th17 and Treg cells
Modify autophagy and apoptosis in epithelial and endothelial cells, macrophages, neutrophils and lymphocytes in the lung and other organs
Up regulate AMPK and PGC-1α, improve mitochondrial function and restore mitochondrial biogenesis and metabolic homeostasis

*Adapted from (Fedson, 2011; Fedson and Opal, 2013; and DS Fedson, unpublished observations).

[a] HO-1 = heme oxygenase-1; TLR = Toll-like receptor; PAMP = pathogen-associated molecular pattern; DAMP = damage associated molecular pattern; NF-kappaB = nuclear factor kappaB; TNFα = tumor necrosis factor alpha; IL-1 = interleukin-1; HMGB1 = high molecular group box-1; RAGE = receptor for advanced glycation end products; eNOS = endothelial nitric oxide synthase; iNOS = inducible nitric oxide synthase; C5aR = C5a receptor; Treg = T regulatory; AMPK = adenosine monophosphate-activated protein kinase, PGC-1α = peroxisome-proliferator-activated receptor (PPAR)γ coactivator-1α.

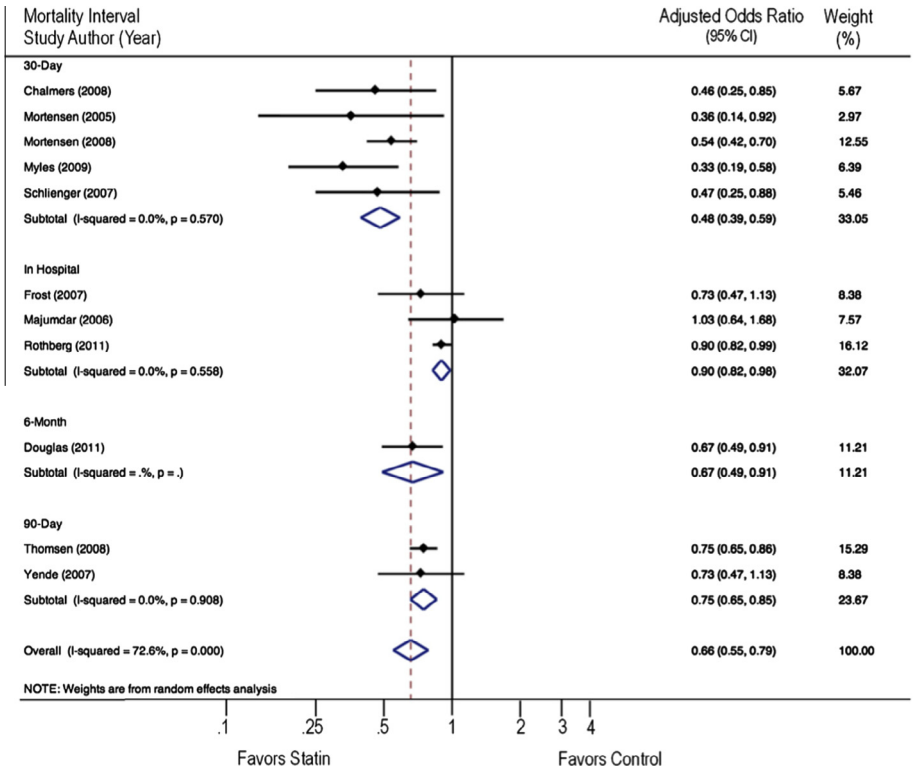

Fig. 5. Forest plot of the adjusted odds ratios (OR) from a meta-analysis of statin effectiveness in reducing all-cause mortality in patients with pneumonia, stratified by intervals at which mortality was reported. The overall adjusted OR was robust; similar results were obtained in sensitivity analyses that considered the type of study design, type of statin, use of propensity scores and adjustment for pneumonia severity, vaccination and smoking status and uncommon covariates (Chopra et al., 2012; reproduced with permission. See Chopra et al. for details on the individual studies included in the meta-analysis).

Table 2
Observational studies of inpatient statin treatment of patients hospitalized with pneumonia.

Study	Diagnostic method	No. patients, ages, source, study years	Treatment ascertainment	Method of analysis	Outcome	Adjusted OR (95% CI)
Yende et al. (2011)	Clinical/X-ray	1895 ⩾18 years 28 hospitals 2001–03	Each patient	Cohort, propensity adjusted	90-day all-cause mortality Severe sepsis	0.73 (.47–1.13) 0.97 (.68–1.40)
Rothberg et al. (2012)	Administrative data	121,254 ⩾18 years 376 hospitals 2003–05	Administrative data on inpatient medications	Cohort, covariate and propensity adjusted	All-cause hospital mortality Non ICU ICU All	 0.79 (.71–.87) 0.93 (.81–1.06) 0.86 (.79–.93)
Mortensen et al. (2012)	Administrative data	11,498/11,498 ⩾65 years 150 hospitals 2002–07	Administrative data, >80% compliance	Case-control, propensity matched	30-day all-cause mortality	0.68 (.59–.78)

There have been no reports of randomized controlled trials of inpatient statin treatment of pneumonia patients. However, a randomized controlled trial in 250 ICU-admitted patients with severe sepsis (approximately half of whom had pulmonary infection) has shown that discontinuing atorvastatin treatment in a subgroup of 77 prior statin users was associated with an increase in 28-day mortality (28% in discontinued users vs. 5% in those with continued statin treatment; $p = 0.01$) (Kruger et al., 2013). This finding is similar to what was found with discontinued treatment in earlier observational studies of patients hospitalized with ACS (Fonarow et al., 2005) and pneumonia (Yende et al., 2011), and it may have been due to rebound hypercytokinemia. Kruger et al. also found that compared with placebo, atorvastatin was not associated with lower levels of IL-6, hospital length of stay, improvement in organ function or mortality. These results were disappointing, but the atorvastatin dose was only 20 mg/day and only four doses (on average) were administered to each patient (Kruger et al., 2013; O'Kane et al., 2013). A higher statin dose and a longer duration of treatment might have improved outcomes. This possibility is suggested by the results of randomized controlled trials of simvastatin pretreatment (40 or 80 mg/day) in inhaled LPS-challenged healthy volunteers (Shyamsundar et al., 2009) and simvastatin (80 mg/day) treatment of acute lung injury patients (Craig et al., 2011). In the latter study, significant improvements in lung injury were seen after 14 but not 7 days of treatment. Nonetheless, other observational studies of pneumonia patients have reported no changes in

plasma cytokine levels (IL-6, IL-10, TNFα) with inpatient statin treatment (Yende et al., 2011) and no effect on hospital mortality in ICU-admitted patients (Rothberg et al., 2012). Moreover, a propensity-matched study of 2743 ICU patients showed that statin treatment within 24 h of admission was associated with a lower but statistically non significant development of ARDS (OR 0.79; 95% CI 0.57–1.10) (Bajwa et al., 2012).

Recently, a randomized controlled trial in 100 statin-naïve patients hospitalized with early sepsis showed that treatment with atorvastatin (40 mg/day) prevented the development of severe sepsis (4% in treated patients vs. 24% in controls; $p = .007$) (Patel et al., 2012). This is an important study because it suggests that instead of limiting immunomodulatory treatment to sepsis and pneumonia patients requiring ICU admission, treatment should be administered to all such patients requiring hospital care.

4.2. Statins and influenza

There are few reports of the effectiveness of outpatient statin treatment on influenza hospitalizations and deaths. The Danish study mentioned above considered influenza vaccination as a confounding variable, but analysed statin effectiveness throughout the year, not during influenza seasons (Nielsen et al., 2012). In a more direct analysis, Canadian investigators conducted a retrospective cohort study using administrative data on older adults gathered over a ten-year period (1996–2006) (Kwong et al., 2009). For each year, all study subjects had received influenza vaccine prior to the onset of the influenza season, thus removing vaccination as a source of bias. The investigators determined the propensity for study subjects to be treated or not treated with statins, and assembled matched cohorts of 1.2 million individuals in each group. In a propensity matched but otherwise unadjusted analysis, outpatient statins were associated with a 13% reduction in all-cause pneumonia and influenza mortality (OR 0.87; 95% CI 0.84–0.89) during broadly defined influenza seasons. When the analysis was restricted to 5-week peak periods of influenza activity and adjusted for the same variables, there was an overall 5% reduction in pneumonia hospitalization (adjusted OR 0.95; 95% CI 0.90–1.00), a 14% reduction in 30-day pneumonia mortality (adjusted OR 0.86; 95% CI 0.75–0.98), and a 9% reduction in all-cause mortality (adjusted OR 0.91; 95% CI 0.86–0.95). The investigators concluded that outpatient statins were "associated with a statistically significant but minimal protective effect against influenza morbidity that can easily be attributed to residual confounding". They added, "Public health officials and clinicians should focus on other measures to reduce morbidity and mortality from the next influenza pandemic" (Kwong et al., 2009). For health officials, such "minimal" protection might be worthwhile. However, despite the impressive size and complexity of this Canadian study, the results are problematic, largely because of uncertainties about the ascertainment of outpatient statin use.

Two observational studies have reported on previous outpatient statin use in patients hospitalized during the 2009 H1N1 pandemic. In a retrospective case-control study of 1520 patients with laboratory-confirmed influenza, outpatient statins were associated with a 28% reduction in the severity of illness (adjusted OR 0.72; 95% CI 0.38–1.33) (Brett et al., 2011). A smaller study of 60 patients hospitalized in a single institution concluded that statin use at the time of admission was associated with lower lung injury scores, although no details of the analysis were presented (Riscili et al., 2011). Unfortunately, neither report included information on inpatient statin treatment.

The effectiveness of statin treatment of patients hospitalized with influenza has been reported in two observational studies. The first study evaluated treatment with several different immunomodulatory agents in a group of 197 patients hospitalized with laboratory-confirmed pH1N1 (Viasus et al., 2011). Unfortunately, too few patients were treated with statins ($n = 12$) to allow meaningful conclusions to be drawn about the results.

I presented the results of the second observational study earlier in Section 1; this is the only study to report that inpatient statin treatment of influenza patients reduced mortality (Vandermeer et al., 2012). The results have been criticized because it is thought that patients who received inpatient statins were "healthy users" (Jackson and Nelson, 2012), but it is difficult to understand how they could have been "healthy users" when they had almost twice as many high-risk conditions as those who were not given statins. More important, if receipt of influenza vaccine defines a "healthy user" (Jackson et al., 2006; Jackson and Nelson, 2012), this potential bias was accounted for by the investigators in their adjusted analysis: the 41% reduction in mortality in statin-treated patients was in addition to any reduction that might have been attributable to previous influenza vaccination and antiviral treatment (Vandermeer et al., 2012). That said, a "healthy user" bias often confounds the results of studies when treatments are taken over long periods of time (Dormuth et al., 2009; Shrank et al., 2011). It is unlikely, however, that such confounding would be a problem for inpatient statin treatment because the effects are evaluated over a period of only a few weeks and the decision to "use" a statin is made by a physician, not the patient.

One important implication of the results of the statins/influenza study must not be overlooked. Future evaluations of the effectiveness of influenza (and pneumococcal) vaccination must consider statins and other potentially effective immunomodulatory agents as confounding variables. Any study that does not do this should be regarded as incomplete.

5. Clinical studies of other immunomodulatory agents

Corticosteroids are often used to treat patients hospitalized with sepsis, severe acute lung injury and acute respiratory distress syndrome because it is believed they will improve survival (Patel and Balk, 2012). The 2009 H1N1 pandemic provided another opportunity to evaluate the effectiveness of steroid treatment. Some investigators found it was not effective and might have been harmful (Annane, 2011; Brun-Buisson et al., 2011; Lim et al., 2011; Martin-Loeches et al., 2011; Matthay and Liu, 2011).

Two recent observational studies of ICU-admitted patients have raised the intriguing possibility that aspirin treatment might benefit critically ill patients. In a retrospective cohort study of 5523 patients with a first episode of systemic inflammatory illness, aspirin was given to 2082 (38%) (Eisen et al., 2012). In a propensity-matched analysis, aspirin treatment was associated with a reduction in hospital mortality from 17.2% to 10.9%, and in 970 patients with culture-proved sepsis, mortality was reduced from 42.2% to 27.4%. Both results were statistically significant. Another (and somewhat confusing) study reported on a prospective cohort of 570 critically ill patients admitted to the ICUs of a single hospital (O'Neal et al., 2011). The results showed that pre-hospital statin use was associated with a 40% reduction in ARDS but no reduction in mortality. In patients whose pre-hospital treatment included aspirin but not a statin, there were no effects on the development of severe sepsis or ARDS, but in those whose pre-hospital treatment include both agents, rates for developing both severe sepsis and ARDS were lowest, suggesting that aspirin may have potentiated the benefits of outpatient statin treatment.

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are used to treat patients with cardiovascular diseases and hypertension. In these patients, increased production of angiotensin II activates the renin-angiotensin-aldosterone system and this is closely associated with vascular inflammation (Di Raimondo et al., 2012). Recently, investigators

evaluated treatment with ACEIs and ARBs to determine their effects on 30-day pneumonia mortality (Mortensen et al., 2012). In a study of 11,498 propensity matched cases and controls, outpatient and inpatient use of ACEIs were associated with 12% and 42% reductions in mortality, respectively (adjusted ORs 0.88 [95% CI 0.80–0.97] and 0.58 [95% CI 0.48–0.69], respectively). For ARBs, the mortality reduction for outpatient use was 27% (adjusted OR 0.58; 95% CI 0.58–0.92), and for inpatient use it was 53% (adjusted OR 0.47; 95% CI 0.30–0.72). Although 3060 study subjects were treated with a statin and either an ACEI or an ARB, no analysis was undertaken to determine the effectiveness of combination treatment. An extensive systemic review and meta-analysis of 37 observational studies and randomized controlled trials concluded that treatment with ACEIs or ARBs reduced the risk of pneumonia and pneumonia-related mortality by approximately 30% (Caldeira et al., 2012). However, few of the observational studies and none of the clinical trials that were reviewed were primarily designed to evaluate the effect of treatment on pneumonia. In addition, the possibility of confounding by statin use was not considered, and none of the studies evaluated inpatient treatment. A more recent nested case-control study found no association between ACEI use and the risk of pneumonia, but no information was provided on the effects of treatment on pneumonia hospitalization or mortality, nor on the effects of inpatient treatment (Dublin et al., 2012). The immunomodulatory potential of ACEIs and ARBs has received less attention that it deserves, especially since several experimental models of acute lung injury have shown that these agents block angiotensin II-induced inflammatory changes and improve survival (Nahmod et al., 2013).

Peroxisome proliferator-activated receptor (PPAR) agonists and adenosine monophosphate-activated kinase (AMPK) agonists are also promising agents for treating influenza (reviewed in Fedson, 2008, 2009a, 2009b, 2011). There is a substantial molecular cross talk between statins and PPARα agonists (fibrates) (Paumelle and Staels, 2008), statins and PPARγ agonists (thiazolidinediones; i.e., glitazones) (Birnbaum et al., 2006; Yano et al., 2007), and statins and AMPK agonists (Wong et al., 2009; Rossoni et al., 2011). There is also considerable cross talk between PPAR agonists and AMPK (Wong et al., 2009; Lee and Kim, 2010). These agents deserve consideration because of their immunomodulatory activities in both experimental and human inflammatory diseases and because they are widely available and familiar to physicians who use them to treat patients with cardiovascular diseases and diabetes mellitus. As yet, no clinical studies have been reported on their effectiveness in treating patients with pneumonia or influenza.

Several other agents with immunomodulatory potential have been suggested for influenza treatment (Darwish et al., 2011). Some are inexpensive generics (e.g., macrolides, cyclooxygenase-2 inhibitors) that have been disappointing in observational studies of human disease. Other agents (e.g., anti-TNF treatment, mesenchymal stem cells, angiopoeitin-1, high mobility group box-1 antagonists) are limited in supply, very costly or still under investigation.

Virtually all discussions of immunomodulatory agents have focused on single agent treatment. However, because of the extensive molecular cross talk between many of these agents, combinations of two or more (statins included) might be more effective than single agent treatment alone (For a more detailed discussion, see Fedson, 2008).

6. Animal models of treating influenza with statins and other immunomodulatory agents

6.1. Statins

Two studies have been published on the efficacy of statin treatment in influenza virus-infected mice. In one report, rosuvastatin was added to the diet of 8-12-week old C57BL/6 mice starting 1 day before they were infected with H3N2 and WSN viruses (Radigan et al., 2012). Treatment had no effect on survival, and based on these results the authors concluded "the association between HMG CoA reductase inhibitors and improved outcomes in patients with sepsis and pneumonia are not attributable to their effects on influenza A infection". However, the dosage of infecting virus used in this mouse study was uniformly lethal and there was clear evidence that mice stopped eating (and being treated) 2 days after they were infected. Given what is known about rebound hypercytokinemia and increased mortality when statins are prematurely discontinued, the failure to demonstrate statin efficacy in this study was pre-ordained. In a much larger study, several different statins were tested in adult (17–21 g) female BALB/c mice infected with several different influenza viruses (Kumaki et al., 2012). Again, the infecting doses of the viruses were highly lethal, and treatment lasted only a few days, stopping at a time when the clinical illness was most severe. No protection from statin treatment was shown or should have been expected.

Recently, investigators have examined the efficacy of treatment with simvastatin, oseltamivir and a combination of the two agents in 6–8-week old female BALB/c mice infected with either a highly pathogenic H5N1 virus or a less pathogenic pH1N1 virus (Belser et al., 2013). Starting three days before infection, simvastatin (10 mg/kg) was administered orally for 12 days, and oseltamivir (50 mg/kg) was given for eight days, starting 24 h before infection. All of the control and simvastatin-treated H5N1-infected mice died, whereas all oseltamivir-treated and combination-treated mice survived. Interestingly, in spite of its lack of effect on survival, simvastatin alone reduced levels of a few inflammatory cytokines and chemokines (e.g., IFNγ, TNFα, IL-10). In pH1N1-infected mice, there were no deaths and few differences in cytokine and chemokine levels in any treatment group.

6.2. Other immunomodulatory agents

Several studies have assessed the efficacy of other immunomodulatory agents in treating mice with influenza virus infections. The first study, published in 2005, evaluated resveratrol treatment in 4-week-old female BALB/c mice infected with the mouse-adapted A/H1N1 (PR8) virus (Palamara et al., 2005). (Resveratrol is a plant-derived polyphenol that is found in the skin of red grapes.) Intraperitoneal treatment was begun one hour after infection and continued daily for the next 7 days. In treated mice, mortality was approximately 20%, whereas it was approximately 60–65% of untreated controls died (Fig. 6a). In addition, resveratrol reduced virus replication in the lungs by 98%. This landmark study established the principle that influenza could be successfully treated with an immunomodulatory agent.

The second report was published in 2007. In this study, female BALB/c mice (6–8 weeks old) were infected with A/influenza (H2N2) virus, and treatment with the PPARα agonist gemfibrozil (60 mg/kg intraperitoneally) was begun four days after infection when the mice were beginning to show signs of illness (Budd et al., 2007). In the treated group ($n = 46$), 52% survived compared with only 26% of control mice ($n = 50$; $p = 0.0026$) (Fig. 6b). No virus studies were undertaken, but the benefit of treatment was indisputable.

The third study was published in 2008 (Zheng et al., 2008). The investigators infected 5–7-week old female BALB/c mice with a high dose (1000 LD_{50}!) of H5N1 virus. In preliminary experiments, intraperitoneal treatment was begun 4 h after infection. All mice treated with zanamivir survived, whereas those treated with a COX-2 inhibitor, gemfibrozil, mesalazine (a PPARγ agonist) or combinations of the COX-2 inhibitor and each of the PPAR agonists died, albeit somewhat later during the course of illness. In the next

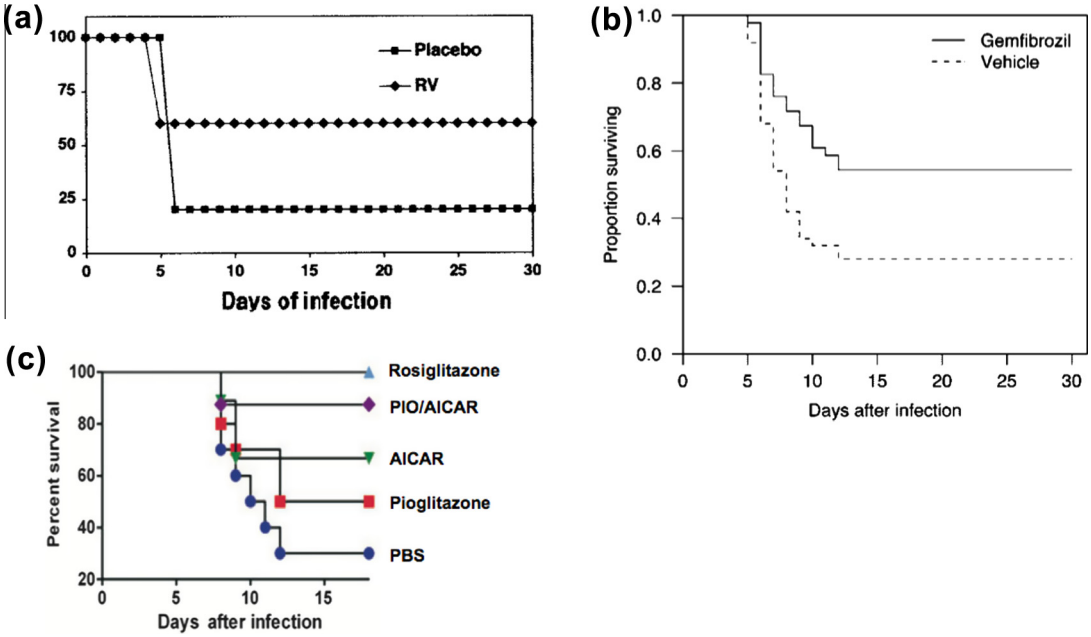

Fig. 6. (a) Effect of resveratrol (RV) treatment on influenza A (PR8) virus infection of *4-week-old* female BALB/c mice. Treatment (intra-peritoneal; 10 mice per group) was begun 1 h after infection and continued daily for 7 days. RV treatment significantly increased percent survival (evaluated daily for 30 days; $p < 0.05$) (Palamara et al., 2005; reproduced with permission). (b) Effect of gemfibrozil on survival of female adult BALB/c mice infected with influenza A/Japan/305/57 (H2N2) virus and treated intraperitoneally once daily (60 mg/kg) from days 4 to 10. Pooled results from four experiments; 50 control and 46 treated mice; $p = 0.0026$ (Budd et al., 2007; reproduced with permission). (c) Effects of treatment with PPARγ and AMPK agonists (begun 3 days before infection and continued daily) on mortality in 8–10-week old female C57BL/6 mice infected with influenza A H1N1 (PR8) virus ($n \geqslant 10$ per group). All treatments significantly increased survival ($p < 0.01$) (Moseley et al., 2010; reproduced with permission).

set of experiments, treatment was begun 48 h after infection. Single agent treatment did not improve survival when compared with antiviral treatment alone (13.3% survival). However, when zanamivir was combined with the COX-2 inhibitor and PPARγ agonist, mortality was substantially delayed and survival improved to 53.3% ($p < 0.02$). These findings offer some encouragement for treating H5N1 infections with immunomodulatory agents, although it is difficult to draw firm conclusions about this study because an antiviral agent was included in each treatment group and, perhaps more important, very high infecting doses of H5N1 virus were used.

Two subsequent studies examined the efficacy of pre-treating PR8-infected C57BL/6J (B6) mice with PPARγ agonists alone or in combination with AICAR, a metformin-like AMPK agonist. In the first study, pioglitazone reduced mortality from 92% to 50% ($p = 0.005$), yet pulmonary virus titers were the same in treated and control mice in the nine days following infection (Aldridge et al., 2009). In the second study, 8–10-week old female C57BL/6 (B6) mice were infected with PR8 virus (Fig. 6c) (Moseley et al., 2010). Pre-treatment with pioglitazone alone, AICAR alone, pioglitazone and AICAR combined or rosiglitazone alone resulted in significant increases in survival compared with controls ($p < 0.01$). Mice were also infected with a uniformly lethal dose of a mouse-adapted pandemic 2009 H1N1 (pH1N1) virus and treated intraperitoneally with rosiglitazone according to the same schedule (Moseley et al., 2010). Treatment resulted in a modest but statistically significant delay in the time of death and a 20% improvement in survival. In another study, pioglitazone showed greater efficacy than dexamethasone in treating smoke-exposed mice infected with H1N1 virus (Bauer et al., 2010).

Other immunomodulatory agents have been tested in mouse models of influenza. Treatment of 6–8-week old C57BL/6, PR8-infected mice with the PPARγ agonist 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) started 1 day after infection reduced mortality by 79% and markedly reduced pulmonary virus levels, but surprisingly, treatment started on day 0 was not protective (Cloutier et al., 2012). Moreover, treatment with rosiglitazone was also not protective, regardless of whether it was started on day 0 or day 1; this result was at odds with the finding that rosiglitazone pretreatment of PR8-infected C57BL/6 mice was effective (Moseley et al., 2010).

Other investigators have studied GSH-C4, a highly active glutathione derivative (Sgarbanti et al., 2011). This agent strongly inhibited PR8 influenza virus replication in vitro by modifying redox-sensitive pathways essential for cytoplasmic maturation of the virus hemagglutinin. In PR8-infected female BALB/c mice (6–8 weeks old), intraperitoneal treatment with GSH-C4, starting one hour after infection and continuing daily for 7 days, reduced mortality from 87% to 48% ($n = 23$ in each study group; $p = 0.001$). Treated mice also had less pulmonary inflammation and lower levels of virus in their lungs. It is known that statins, glitazones, fibrates and metformin all up regulate glutathione activity (Singhai et al., 2011).

Several conclusions can be drawn from the results of these experimental studies of statins and other immunomodulatory agents. First, the two published studies of statins in influenza-infected mice do not represent fair tests of treatment for several reasons, including highly lethal infecting doses of virus and an inadequate course of treatment. Second, several other agents have shown protection against infection with several different influenza viruses, and treatment begun after infection has reduced mortality. Third, whenever it has been examined, treatment has had no effect on (or it has reduced) virus replication in the lungs of infected animals. Finally, all but one of these studies (Zheng et al., 2008) evaluated treatment with agents not known to have antiviral activities.

One final observation is worth mentioning. Immunomodulatory treatment of severe influenza might be able to "roll back" the damaging and sometimes fatal host response of adults to the more benign, non-fatal response of children (Fedson, 2009b). In a study of

the highly inflammatory host response to hepatic ischemia reperfusion injury in mice, pre-treatment with rosiglitazone suppressed the often fatal inflammatory response of "young adult" mice, making it more like the milder inflammatory response seen in "children" (Shin et al., 2008). The implications of this study for immunomodulatory treatment of influenza and other types of critical illness have been ignored, but I believe its importance could be far-reaching.

7. Understanding the immunopathogenesis of influenza and its relationship to immunomodulatory treatment

The immunopathogenesis of severe and fatal influenza has been reviewed by many virologists whose experimental studies form the basis for our understanding of influenza virus/host interactions (Fukuyama and Kawaoka, 2011; Gorski et al., 2012; Korth et al., 2012; Kuiken et al., 2012; Medina and Garcia-Sastre, 2011; Peiris et al., 2010; Josset et al., 2012; Tisoncik et al., 2012). The details of their studies are beyond the scope of my review. Nonetheless, several aspects of their perspectives on influenza pathogenesis are relevant to my discussion.

7.1. The perspective of influenza virologists

Clinical observations in adults and children with pH1N1 influenza show that patients with critical illness initially have a highly inflammatory response, but later during the second week, when most patients die, the response is dominated by immunosuppression (Agrati et al., 2010; Lee et al., 2011; Hall et al., 2013). This pattern is similar to what has long been known for sepsis (Wang and Deng, 2008). However, a recent genomic study of the human leukocyte response to trauma, another acute critical illness associated with severe inflammation, showed that both pro-inflammatory and anti-inflammatory cytokines were present simultaneously over the entire course of illness (Xiao et al., 2011). In addition, an experimental study of bacterial sepsis in mice showed that the mixed pro- and anti-inflammatory cytokine responses in mice that lived and those that died were similar throughout the course of illness up until 48 h before death (Osuchowski et al., 2012). Thus, factors that distinguish between severe and fatal disease appear to be differences of degree, not kind, and survival appears to depend on an eventual return to homeostasis. Moreover, even in mild illness, host factors have been shown to be primary determinants of outcome: for example, following human challenge of healthy individuals with the same dose of H1N1 virus, major differences in genomic signaling were seen in symptomatic compared with asymptomatic subjects (Huang et al., 2011).

In animal studies, influenza virologists have documented changes in innate immunity and an early increase in pro-inflammatory cytokines (i.e., "cytokine storm") (e.g., Maines et al., 2012; Tisoncik et al., 2012). This is followed by an adaptive phase that, in fatal illness, overwhelms the host (Hatta et al., 2010; Perrone et al., 2010). This reparative or recovery phase of the disease has received increasing attention from influenza virologists (e.g., Marcelin et al., 2011; Shinya et al., 2012; Josset et al., 2012). Many virologists have concluded that the best way to ensure recovery is to shut down virus replication (e.g., Boon et al., 2011; Gorski et al., 2012).

Some investigators have argued that disrupting cell signaling pathways necessary for influenza virus replication could have antiviral effects that would obviate the risk of antiviral resistance (Ludwig, 2011). However, any agent that disrupts signaling in influenza virus-infected cells would probably have important signaling effects on other cells and organs that are not infected.

Interrupting virus replication is not always necessary to improving outcomes in influenza virus infection. Several virologists have compared influenza virus infection in normal mice and in mice with altered immune systems (e.g., cytokine knockout), and shown that survival rates differ greatly but levels of virus replication are the same (e.g., Lin et al., 2011; Abdul-Careem et al., 2012; Berri et al., 2013). Influenza virologists usually focus their attention on changes in innate immune cells in the pulmonary airways and alveoli (macrophages and neutrophils and NK, dendritic and CD4+ and CD8+ T cells) (McGill et al., 2009). They have given less attention to other aspects of the host response, including: (1) redox signaling (Imai et al., 2008; Vlahos et al., 2012); (2) active resolution of inflammation (Cilloniz et al., 2010; Prieto et al., 2010; Serhan, 2011; Walker et al., 2011); (3) endothelial cell function (Maganto-Garcia et al., 2011; Griffin et al., 2012; Reddy et al., 2012; Teijaro et al., 2011) and pulmonary microvascular barrier integrity (London et al., 2010; Armstrong et al., 2012; Steinberg et al., 2012; Zeng et al., 2012); (4) early mitochondrial biogenesis (Carre et al., 2010; Piantadosi et al., 2011; Piantadosi and Suliman, 2012); and (5) changes in energy metabolism (McCall et al., 2011; Liu et al., 2012; Rathmell, 2012; Verbist et al., 2012). They have also overlooked the inflammatory response following influenza virus infection that is triggered by cellular debris alone (e.g., Damage-Associated Molecular Patterns [DAMPs]) (Lietzen et al., 2011; Kaczmarek et al., 2013; Tolle and Standiford, 2013), and ignored the important finding that severe acute lung injury can be caused by *inactivated* H5N1 influenza virus (Imai et al., 2008).

7.2. Treating the host response, systems biology and the contributions of clinicians

Studies of experimental acute lung injury and its associated multi-organ failure (e.g., Fagnoul et al., 2013) strongly suggest that many critical aspects of the host response to influenza virus infection can probably be modified and improved by treatment with immunomodulatory agents (for more detailed discussion, see Fedson, 2008, 2009a, 2009b, 2011): statins (Jacobson, 2009; Lee and Kim, 2010; Planaguma et al., 2010; Takano et al., 2011; Grommes et al., 2012a; Lee et al., 2012; Singla and Jacobson, 2013), ACE inhibitors and angiotensin receptor blockers (Di Raimondo et al., 2012; Nahmod et al., 2013), PPAR agonists (Grommes et al., 2012b; Drosatos et al., 2013) and AMPK agonists (Zmijewski et al., 2008; Lee and Kim, 2010). Some of these agents might even work synergistically with corticosteroids to improve patient outcomes (Bougarne et al., 2009; Matthews et al., 2009; Maneechotesuwan et al., 2013).

Several years ago, investigators pointed out that targeting the host response with immunomodulatory agents would be complex, and more research was needed in order to "shed light on the complex, redundant and finely balanced nature of the innate immune system. Such areas include systems biology and translational approaches to deciphering innate immunity, and particularly TLR biology, deciphering the impact of modulators regulating inflammation, and of regulatory molecules balancing inflammatory responses, and deciphering the complex mechanisms of key human genetic mutations that alter disease susceptibility. This information is *imperative* (italics added) to enable the orderly and safe development of effective therapies ..." (Brown et al., 2007). A critic of systems biology has pointed out that a reductionist perspective like this overlooks the "critical utility of key concepts from physiology like homeostasis, regulated systems and redundancy as major intellectual tools to understand how whole animals adapt to the real world" (Joyner, 2011). He added, "it is a failure of regulation at multiple levels that causes many common diseases".

To summarize, until now the influenza virologist's perspective on the pathogenesis of severe and fatal influenza outlined above

has governed our approach to patient management and public health pandemic preparedness. Although some of these virologists are beginning to understand that late immunosuppression, not an early "cytokine storm", might be the more important factor in determining outcome, few accept the notion that modifying the host response alone without controlling virus replication could improve survival. Few recognize that laboratory and clinical investigators in other fields (e.g., cardiovascular and metabolic diseases) have made contributions to understanding the host response to critical illness, or accept this knowledge as being every bit as important to understanding influenza pathogenesis as the contributions of influenza virologists themselves. Some influenza virologists place their hopes on treatments that subvert cell signaling pathways necessary for virus replication (instead of targeting the virus itself), but these treatments will surely affect cells and organs that are not infected. It is possible that the keys to improving survival could be found in restoring endothelial barrier integrity and accelerating mitochondrial biogenesis in non-infected cells and organs. Finally, I believe it is important to acknowledge that clinical investigators who study patients, not systems biologists who study influenza viruses, have given us the first practical suggestions on how to manage the dysregulated host response seen in patients with severe influenza.

The laboratory and clinical findings reviewed here prompt a question – how much information must be gathered *before* we decide whether to study or use a new treatment in influenza patients? Perhaps we could base our decision on having observed clinical improvement after using a safe and familiar agent to treat patients with another disease (e.g., ACS) characterized by similar disturbances in the host response. If so, research could then explain the mechanisms for how the benefits of treatment had been achieved *after* they had been demonstrated. It might turn out that agents shown to increase survival do so by improving the host's ability to tolerate an otherwise fatal infection (Medzhitov et al., 2012).

8. A research agenda for immunomodulatory treatment of influenza

Several years ago I published a five-point research agenda on immunomodulatory treatment of influenza (Fedson, 2009a,b). Although its basic outline remains unchanged, newer information suggests several ways in which it could be modified and improved.

8.1. Animal models

Animal models of influenza virus infection have provided detailed information on the interaction of the virus with the host, but in most instances the models have not reflected the specific features of human influenza. As shown in Table 3, studies of statins and other immunomodulatory agents might be more informative if the models better reflected host factors associated severe disease in humans. For example, there are important differences in the responses of BALB/c mice (which have a Th-2 bias) and C57BL/6 mice (which have a Th-1 bias) to pH1N1 and H5N1 infections (Otte et al., 2011). Using another strain of mouse (e.g., DBA/2J) that is more susceptible to a lower infectious dose and develops a greater, more human-like inflammatory response to infection might be more informative (Warren et al., 2010; Boon et al., 2011; Pica et al., 2011). Investigators might use mice with conditions associated with altered immunity such as obesity and diabetes (Smith et al., 2007; Easterbrook et al., 2011; O'Brien et al., 2012), cardiovascular disease (Naghavi et al., 2003) and pregnancy (Marcelin et al., 2011; Rowe et al., 2011; Pazos et al., 2012). The use of mouse-adapted strains of more recent human viruses (e.g., pH1N1 or H5N1), and lower infecting doses ($\leqslant LD_{50}$; e.g., Palamara et al., 2005; Budd et al., 2007) might better reflect case fatality rates seen in human H5N1 influenza, the 1918 pandemic and severe seasonal influenza. Investigators could also study combination treatment regimens (Combo-Paintlia et al., 2006; Chen et al., 2008), compare treatment with these newer agents and steroids (Bauer et al., 2010), and evaluate their effects on secondary bacterial pneumonia. All of these studies should include pre- and post-pubertal mice of both sexes. Once the most promising immunomodulatory agents (or combinations of agents) had been identified, they could then be tested in ferrets and perhaps in non-human primates. In this way, a rational choice could be made on which agent(s) should be evaluated in randomized controlled trials in human influenza.

8.2. Clinical and epidemiological research

Intensive care investigators have been interested in organizing randomized controlled trials of statin treatment of ICU-admitted influenza patients (InFACT Global H1N1 Collaboration, 2010; STIP: Statins Trial for Influenza Patients, NCT00970606). However, observational studies of patients with sepsis and pneumonia indicate that statins might not be very effective if treatment is limited only to the most seriously ill, ICU-admitted patients (Novack et al., 2009; Terblanche et al., 2011; Yende et al., 2011; Rothberg et al., 2012). Instead, it might be better to treat all patients hospitalized with influenza in order to prevent progression to more severe disease (Patel et al., 2012). Until clinical trials are undertaken, investigators could still obtain valuable information on statins and other immunomodulatory agents by studying their acute pharmacokinetics and their effects on biomarkers of immune dysfunction in patients hospitalized with critical illness due to seasonal influenza, pneumonia and sepsis (Kruger et al., 2009; Shyamsundar et al., 2009; Craig et al., 2011). Documenting the effects of treatment in human volunteer studies that model of acute inflammation might also be helpful (Shyamsundar et al., 2009).

Better observational studies are needed on inpatient treatment with statins and other immunomodulatory agents of patients with influenza, pneumonia and sepsis. Investigators must document whether patients were treatment naïve or were continuing outpatient treatment, which specific agents were used, when they were started, and how long treatment was given. Attention must be given to comparing single agent with combination treatment (e.g., statins and ACEIs or ARBs) and to evaluating relationships between treatment and underlying conditions known to be associated with altered immunity (e.g., metabolic syndrome). Large databases of

Table 3
Characteristics of human influenza, conventional mouse models of influenza and newer mouse models for studies of immunomodulatory treatment.

Factor	Human influenza	Conventional mouse models	Newer mouse models
Genetic background	Heterogeneous	Specific strain, (C57Bl/6, BALB/c)	More human-like strain (e.g., DBA/2J)
Immune status	Usually altered, e.g., metabolic syndrome	Immunological homeostasis, cytokine KO	Altered immunity (pregnancy, DIO, ob/ob, db/db, ApoE$^{-/-}$)
Age and sex	All ages, both sexes	Usually young adults (e.g., 6–10 weeks old)	Children vs adults, both sexes
Virus dose	Usually unknown	Often high dose	Lower dose ($\leqslant LD_{50}$)
Virus strain	H1N1, H3N2	Often highly mouse adapted (PR8)	Adapted human viruses (pH1N1, H5N1)

hospital care could be especially useful to epidemiologists, allowing them to establish associations between underlying conditions such as diabetes and inpatient treatment with metformin or glitazones. Finally, as I previously recommended (Fedson, 2009a,b), networks of clinicians must organize protocols for clinical trials of immunomodulatory agents in advance of seasonal epidemics and the next pandemic. Sponsorship and funding from government or non-governmental institutions will be critically important. As shown in 2009, without such planning and support, nothing will get done. The importance of these principles has been acknowledged by senior health officials in the US (Lurie et al., 2013). The absence of any effort by these health officials to replicate the Vandermeer et al. study during the 2012–2013 seasonal influenza epidemic is a sobering reminder that such planning and support are essential (DS Fedson, unpublished observations).

9. Immunomodulatory treatment and global public health

9.1. Challenges to pandemic vaccination in 2009

The global mortality burden of influenza is uncertain, but most agree that seasonal epidemics cause tens if not hundreds of thousands of deaths each year. Epidemiologists estimate that if a pandemic comparable in severity to the pandemic of 1918 had occurred in 2004, it would have killed 62 million people worldwide, most of them in developing countries (Murray et al., 2006). For more than a decade, the possibility of an H5N1 pandemic has been viewed as a threat not only to global public health but also to national and international security (Kamradt-Scott and McInnes, 2012). In the US, the National Intelligence Council views a global pandemic as one of eight potential "black swan" events that could dramatically alter the landscape for world security (National Intelligence Council, 2012).

The 2009 H1N1 pandemic was widely considered to be mild, yet it is estimated to have infected a quarter of the human population (Van Kerkhove et al., 2013) and caused 400,000 influenza-associated respiratory and cardiovascular deaths worldwide, 80% of them in persons <65 years of age and half of them in Southeast Asia and Africa (Dawood et al., 2012). In response to the pandemic, the World Health Organization (WHO) and most government health agencies recommended widespread pandemic vaccination and antiviral treatment. Yet, in spite of these efforts, scientists, companies and health agencies were unable to develop (Robertson et al., 2011), produce (Partridge and Kieny, 2010) and distribute affordable supplies of pandemic vaccines and antiviral agents in time to affect the outcome of pandemic illness for more than 90% of the world's people (Abelin et al., 2011; Fisher et al., 2011; Monto et al., 2011; Ropero-Alvarez et al., 2012). In the US – a country better prepared than most - vaccination is estimated to have prevented fewer than 2–4% of pandemic cases, hospitalizations and deaths (Borse et al., 2013). Rich countries received supplies of pandemic vaccines before poor countries, and WHO-donated vaccines arrived last of all. Disparities in vaccine deliveries among nations were dramatic; for example, in December 2009, when the US was in the midst of distributing 65–70 million doses of pandemic vaccines, Mexico received its first 835,000 doses (D.S. Fedson, unpublished observation). In all countries, most vaccine deliveries arrived too late to do much good, and millions of doses had to be destroyed.

The global capacity to produce seasonal influenza vaccines has expanded dramatically within the past few years (Palache, 2011), but global demand for these vaccines has fallen far short of the capacity to produce them. Even so, WHO still anticipates a global shortfall in vaccine supply for the next pandemic (Partridge and Kieny, 2013), and greater production capacity alone will not guarantee the supply of pandemic vaccines for everyone in need. Regulatory restrictions and delays, cost factors and huge logistical considerations will still limit what can be done. In all likelihood, the global vaccination response to the next pandemic will be similar to the response in 2009.

9.2. Threats to H5N1 virus surveillance and research

The vulnerability of a conventional vaccine approach to the pandemic threat became apparent in 2007 when the Indonesian Minister of Health decided to stop sharing samples of human H5N1 virus isolates with WHO influenza laboratories unless WHO could guarantee Indonesia a supply of H5N1 vaccines. The 2009 pandemic experience showed how difficult this would be (Elbe, 2010; Fidler, 2010; Wilson et al., 2010). In 2011, WHO announced a new framework for virus sharing and improved access to pandemic vaccines for developing countries (Fidler and Gostin, 2011; World Health Organization, 2011). Whether the WHO framework will improve developing country access to pandemic vaccines remains an open question.

The pandemic threat came to public attention once again in December 2011, when the National Science Advisory Board on Bioterrorism (NSABB) in the US recommended that influenza virologists not publish the full results of their H5N1 transmissibility research (Keim, 2012). Reluctantly, the virologists declared a moratorium on their research (Fouchier et al., 2012), although later the NSABB allowed the results to be published (Herfst et al., 2012; Imai et al., 2012). After a one-year delay, influenza virologists announced they would resume their H5N1 transmissibility research (Fouchier et al., 2013). In the meantime, the US government began revising its oversight procedures for "dual use research of concern".

Influenza virologists are convinced that their H5N1 transmissibility research will have practical benefits for virus surveillance, vaccine development and public health decision-making (Imai et al., 2012). Biosecurity experts, however, believe that tighter restrictions on this research will make the world more secure. Both groups acknowledge that a highly transmissible and virulent pandemic virus could emerge in nature, and solid experimental evidence supports this possibility (Webster and Campbell, 1974; Illyushina et al., 2010; Ye et al., 2010; Jayaraman et al., 2011; Schrauwen et al., 2011; Chen et al., 2012). Mathematical modellers are convinced that a mutant H5N1 virus that is easily transmissible by respiratory droplets could evolve within a mammalian host, and they regard this possibility as a serious global threat (Russell et al., 2012). Tellingly, no influenza scientist or the biosecurity expert has offered a single practical suggestion on what should or could be done if this happens (Fedson and Opal, 2012, 2013).

9.3. The potential for syndromic treatment of acute critical illness

There is a good possibility that statins and other immunomodulatory agents might be used to treat not only patients with influenza, but also those with critical illness due to other infectious and non-infectious diseases; for example, pneumococcal infections (Rosch et al., 2009; Stegenga et al., 2009; Boyd et al., 2012; Doshi et al., 2012), cerebral malaria (Boggild et al., 2009; Reis et al., 2012; Serghides, 2012), trauma (Sauerbeck et al., 2011) and severe burn injury (Elijah et al., 2012). A randomized controlled trial of statin treatment of patients with dengue is underway in Vietnam (Whitehorn et al., 2012). Used in this way, immunomodulatory agents would provide syndromic treatment for critical illness in much the same way as oral rehydration solution (ORS) is used in the syndromic treatment of acute diarrheal illness regardless of microbial cause (Santosham et al., 2010). For patients with pneumonia and sepsis due to any cause, the health impact of these

agents could extend far beyond the benefits they might bring to the management of patients with severe seasonal and pandemic influenza.

The immunomodulatory agents that I have discussed in this review – statins, ACEIs, ARBs, PPAR agonists and AMPK agonists – are currently produced as inexpensive generics in developing countries. Cipla, a large generic pharmaceutical company in India, produces generic statins (simvastatin, atorvastatin), ACEIs (captopril, enalapril, lisinopril), ARBs (irbesartan, olmesartan, telmisartan), pioglitazone, fenofibrate and metformin, and distributes its products to more than 180 countries (see www.cipla.com). Thus, if any one of these agents were shown to reduce influenza mortality, it would be available to people living in any country with a basic health care system. In a developing country, the cost of treating an individual patient would be approximately $1.00, and treatment could be given to rich and poor alike on the first pandemic day.

10. Synthesis and conclusions

Individuals differ in their responses to influenza; most experience mild to moderate illness, others become severely ill and a few die. Most of those who are at increased risk of influenza-related mortality share the common characteristic of chronic low-grade inflammation associated with metabolic syndrome. The mechanisms that account for their vulnerability are only partially understood. Moreover, the influenza virus that caused the 1918 pandemic was unusually virulent, but infection caused low mortality in children and high mortality in young adults. This disparity was not unique; it has also been seen in other acute infectious and non-infectious conditions. The transition from low to high mortality occurs in the second decade of life, and probably reflects an evolutionarily determined transition from pre-pubertal growth to post-pubertal reproduction. Again, the mechanisms that account for this change are unknown. Considered together, these observations indicate that host factors are dominant determinants of outcome in influenza.

Treating patients with cardiovascular diseases with statins modifies the inflammatory phenotype associated with metabolic syndrome and improves survival. Investigators have demonstrated similar phenotypic benefits in treating patients with sepsis, pneumonia and influenza. These benefits are not unique to statins; similar improvements have been seen in animal models and/or patients with pneumonia and influenza following treatment with other agents (e.g., ACEIs, ARBs, glitazones, fibrates, metformin). Thus, the host response to critical illnesses can be changed and outcomes improved by immunomodulatory treatment. There is even the possibility that such treatment could "roll back" the harmful inflammatory response of an adult to the more benign response of a child.

Influenza virologists have found it difficult to accept the idea that treatment could be effective without targeting the virus, yet experimental studies show that the host response to influenza can be modified in ways that improve survival without changing levels of virus replication. In many instances, immunomodulatory agents are effective because they target non influenza virus-infected cells and organs. In doing so, they maintain pulmonary endothelial barrier integrity, accelerate early mitochondrial biogenesis or alter immunometabolism. Overall, treatment seems to promote a return to a state of self-regulated homeostasis that ensures survival.

WHO, other international agencies and national governments continue to base their approach to pandemic preparedness on vaccination and antiviral treatment. The 2009 influenza pandemic dramatically demonstrated the inability of this "top down" approach to meet the needs of global public health. In the foreseeable future, it is unlikely that the same approach will be effective in confronting a new pandemic virus; for example, the influenza A (H7N9) virus (Uyeki and Cox, 2013; Osterholm et al., 2013). Statins and other immunomodulatory agents represent a "bottom up" alternative approach to managing seasonal and pandemic influenza (Fedson and Dunnill, 2007), but we need new types of laboratory and clinical research to determine whether these agents will work. This research must focus primarily on discovering better ways to manage patients, not explaining mechanisms of disease. If it shows that any of these agents is effective, ordinary physicians working in ordinary health care systems throughout the world would have the means to reduce influenza-related mortality.

In an essay published in 1946, George Orwell wrote, "To see what is in front of one's nose needs a constant struggle" (Orwell, 1946). Although influenza scientists have made remarkable contributions to understanding the virus and the disease, during the 2009 pandemic vaccines and antiviral agents were available to only a small proportion of the world's population, and there is no reason to expect them to be more widely available for the next pandemic. Influenza scientists and health officials have focused on developing vaccines and antivirals to manage severe seasonal and pandemic influenza. Nonetheless, it is possible that mortality could be reduced by treating patients with immunomodulatory agents. The need for a new approach of this type is obvious and inescapable.

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