Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola

David S. Fedson

Formerly, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, USA
Correspondence to: David S. Fedson, MD. 57, chemin du Lavoir, 01630 Sergy Haut, France. Email: dfedson@wanadoo.fr.

Abstract: There is an ongoing threat of epidemic or pandemic diseases that could be caused by influenza, Ebola or other emerging viruses. It will be difficult and costly to develop new drugs that target each of these viruses. Statins and angiotensin receptor blockers (ARBs) have been effective in treating patients with sepsis, pneumonia and influenza, and a statin/ARB combination appeared to dramatically reduce mortality during the recent Ebola outbreak. These drugs target (among other things) the endothelial dysfunction found in all of these diseases. Most scientists work on new drugs that target viruses, and few accept the idea of treating the host response with generic drugs. A great deal of research will be needed to show conclusively that these drugs work, and this will require the support of public agencies and foundations. Investigators in developing countries should take an active role in this research. If the next Public Health Emergency of International Concern is caused by an emerging virus, a “top down” approach to developing specific new drug treatments is unlikely to be effective. However, a “bottom up” approach to treatment that targets the host response to these viruses by using widely available and inexpensive generic drugs could reduce mortality in any country with a basic health care system. In doing so, it would make an immeasurable contribution to global equity and global security.

Keywords: Emerging viruses; Ebola; influenza; sepsis; statins; angiotensin receptor blockers (ARBs); angiopoietin (Angpt); angiotensin-converting enzyme 2 (ACE2); WHO

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Introduction

For almost two decades, leading scientists and health officials have warned that we must prepare for a potentially devastating global pandemic of an infectious disease. Initial concern was focused on the avian influenza A (H5N1) virus. More recently, people in West Africa have endured a devastating outbreak of Ebola virus disease. Several other emerging viruses are believed to seriously threaten global health and global security. To prepare, scientists have been urged to discover new vaccines and treatments for these emerging viruses. At the same time, political leaders have been urged by global health experts to invest millions in a “top down” restructuring of the global health system.

This article takes a different view. It focuses on an alternative approach to the scientific discovery of treatments for individual patients, reviews the mechanisms of action and clinical experience with specific drugs that might be useful, and considers whether or not recent lessons regarding this “bottom up” approach to treatment have been learned.

Reductionist science and the discovery of new treatments

In a recent report, van Vught and colleagues sought to explain why hospitalized patients are susceptible to nosocomial pneumonia (1). They assumed that one reason might be immune suppression caused by the conditions for which they had been hospitalized. To address this question, they compared the systemic host responses of ICU patients with hospital-acquired and community-acquired pneumonia (HAP and CAP, respectively). They measured 19 plasma biomarkers and determined genome-wide gene expression
profiles for the two groups. To their surprise, they found
that levels of inflammatory cytokines and endothelial and
cogulation responses in the two groups were similar, as
were most measures of clinical outcome. Although some of
the biomarker responses in HAP patients were “modestly mitigated” (under-expression of type 1 interferon and
elevated expression of “cell junction and mobility gene
signatures”), subgroup analyses, including the presence or
absence of COPD and the type of infection, confirmed the
overall findings (1). Not surprisingly, HAP patients were
admitted to the ICU later (mean 8 days) than CAP patients
(mean 0 days), but mortality rates in the two groups were
not statistically different. Although overall clinical outcomes
were similar in HAP and CAP patients, no information was
provided on whether host responses were different in those
who survived compared with those who died.

The study by van Vught et al. adds to our understanding
of the many mechanisms involved in the host response to
infection. Like most descriptive studies, it provides scientific
explanations for what happens, yet offers no guidance on
how to improve outcomes in patients with pneumonia,
sepsis and other forms of critical illness. More than 100
clinical trials have been undertaken to test drugs designed
to modify individual signaling molecules or pathways
involved in the host response to sepsis (2). None of these
trials has led to meaningful improvement in patient survival.
Suggestions to improve the research model have included (I)
identifying plausible targets for intervention; (II) improving
patient selection, stratification and staging; (III) developing
new designs for early phase studies; and (IV) creating
new large-scale collaborative groups of investigators (2).
Nonetheless, plausible targets for intervention have almost
always been chosen based on findings in animal models that
focused on individual molecules (e.g., TLR4), pathways (e.g.,
coagulation) or systems (e.g., innate immunity) known to be
associated with adverse outcomes. These choices reflect an
approach to discovery that seeks incremental improvements
in scientific understanding. It is epitomized most recently
by systems and computational biology. The study by van
Vught et al. is a good example of this reductionist approach
to discovery.

**A different approach to discovering new treatments**

A different approach to therapeutic discovery moves in the
opposite direction. It starts with the recognition that a
beneficial clinical phenotype has already been observed with
treatment, and it then uses the tools of reductionist science
to investigate the mechanism(s) that brought this about. It
is important to understand that although this alternative
is informed by the discoveries of reductionist science, it
is driven primarily by an unwavering focus on the clinical
(phenotypic) benefits that have been (or seem to have been) achieved with treatment. In effect, it exemplifies a
Darwinian approach to therapeutic discovery.

A good example of this approach is the propensity-
matched observational studies of Mortensen and colleagues
(3,4). They studied patients hospitalized with community-
acquired pneumonia who had been treated with statins
and angiotensin receptor blockers (ARBs). In their initial
study (3), outpatient treatment with either a statin or
an ARB prior to hospitalization was associated with an
approximately 30% reduction in 30-day all-cause mortality,
and inpatient treatment with either drug was similarly
or more effective (Table 1). In a more recent study using
slightly different methodology, outpatient treatment with a
combination of the two drugs was 60% effective in reducing
30-day all-cause mortality (Table 1) (4).

A large body of earlier experimental and clinical research
had suggested that statins and ARBs might be effective
in treating pneumonia patients. These drugs had been
developed by cardiovascular scientists to treat patients with
heart disease (statins) and hypertension (ARBs). Gradually,
investigators realized they also had broad anti-inflammatory
and immunomodulatory (pleiotropic) activities that
affected, among other things, inflammatory and anti-
inflammatory cytokines and chemokines, the complement
cascade, coagulation factors, oxidative stress, macrophage
and T cell polarization, late mediators of inflammation
[e.g., high mobility group box 1 (HMGB1), specialized
pro-resolving mediators of inflammation (e.g., lipoxins,
resolvins), mitochondrial biogenesis and energy metabolism
(5,6)]. These factors are now acknowledged to actively affect
the host response to sepsis (7), pneumonia (8), and other
forms of acute critical illness. Furthermore, cardiovascular
investigators have published more than 80 reports showing
that combination statin/ARB treatment is more effective
than treatment with either agent by itself (9,10; DS Fedson,
unpublished observations).

A full discussion of the many drugs (including PPAR and
AMPK agonists) that might be useful in modifying the host
response to critical illness, and the mechanisms by which they
might act, is beyond the scope of this article. Instead,
the focus will be on treatment with statins and ARBs and
how they affect the host response.
There is growing recognition that endothelial dysfunction and the loss of endothelial barrier integrity are central to the pathophysiology of bacterial sepsis and acute lung injury (7,11,12). Many systemic virus diseases (13), including influenza (14), dengue and Hantavirus pulmonary syndrome (15), are also characterized by endothelial dysfunction. Figure 1 shows the vascular endothelium in its resting state (on the left) and many of the changes in endothelial cell function that occur with sepsis (on the right) (7). The disruption of tight junctions between endothelial cells leads to a loss of barrier integrity, followed by the leak of fluid from the blood into interstitial tissues and beyond (e.g., the alveoli in pneumonia). Inflammatory changes facilitate the recruitment of macrophages and neutrophils that adhere to and transition through the endothelium. These and other changes activate the coagulation cascade, which in turn further stimulates inflammation and often establishes a feed-forward cycle in which more inflammation causes even more endothelial injury. Some of the signaling molecules involved in maintaining endothelial barrier integrity and in its disruption are shown in Figure 1 (7). Others that play important roles in endothelial cell signaling include the angiopeptin (Angpt)/Tie2 signaling axis, angiotensin-converting enzyme 2 (ACE2), vascular endothelial cadherin (VE-cadherin), claudins, C3a/C5a, RhoA/Rac1 GTPases, matrix metalloproteinases (MMPs), and sphingosine-1-phosphate-1 (S1P1) (7,8,11,12). Many other facets of endothelial activity are also involved, including redox metabolism (16) and mitochondrial function (17,18).

Epithelial cell dysfunction is also a well-known feature of the host response to critical illness. Several abnormalities, including a loss of barrier integrity, increased permeability, epithelial apoptosis and increased levels of biomarkers, have been observed in the lung, liver, kidney and gastrointestinal tract (19). Despite the anatomic closeness of epithelial and endothelial cells, it is unclear to what extent functional disturbances in these two cell types are unique or shared. Many treatments being developed for endothelial dysfunction could also affect similar disturbances in epithelial cells. This might be especially important for understanding how treatments for influenza and Ebola virus disease work, as discussed below.

### Statin and ARB effects on endothelial and epithelial dysfunction

Several of the signaling molecules and pathways associated with disrupting or protecting the endothelial barrier are shown in Table 2 (7,12). Treatment with statins and ARBs appears to benefit patients with sepsis, pneumonia, influenza and other forms of critical illness, and may do so by maintaining or restoring endothelial (and perhaps epithelial) barrier integrity. Statins and ARBs are known to affect endothelial cells (for example, 20-24). Their benefits involve (at least in part) the Angpt/Tie2 and ACE2/angiotensin-(1-7)/Mas signaling axes.
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**Figure 1** Changes in the VE response to inflammatory stimuli during sepsis. The resting vascular endothelium is shown on the left in its natural state. As shown on the right, sepsis produces profound changes that convert the endothelium to a procoagulant state. This disrupted endothelium expedites the loss of fluid through disengaged tight junctions and expedites the recruitment, attachment and extravasation of inflammatory cells through the endothelium. Activation of the coagulation cascade potentiates inflammation and completes a vicious cycle in which inflammation induces and exacerbates coagulopathies and endothelial injury. Only some of the signaling molecules involved in maintaining endothelial barrier integrity are shown in the figure. Others that play important roles include Angpt/Tie2 signaling, the ACE2/angiotensin-(1-7)/Mas signaling axis, C3a/C5a, RhoA/Rac1 GTPases, matrix metalloproteinases, and S1P1. ESL1, E-selectin ligand 1; ICAM1, intercellular adhesion molecule 1; LFA1, lymphocyte function-associated antigen 1; MPO, myeloperoxidase; NO, nitric oxide; PAF, platelet-activating factor; PAI-1, plasminogen activator inhibitor 1; PG12, prostaglandin I2; PMN, polymorphonuclear leukocyte; PSGL1, P-selectin ligand 1; ROS, reactive oxygen species; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; t-PA, tissue plasminogen activator; TXA2, thromboxane A2; ACE2, angiotensin-converting enzyme 2; Angpt, angiopoietin; S1P1, sphingosine-1-phosphate-1. [Reprinted with permission (7)].

**Angpt/Tie2 signaling**

The molecular biology of the Angpt/Tie2 signaling axis has been revealed in studies spanning more than a decade (25-28). Angpt-1 is found in platelets, pericytes and especially in endothelial cells, where it acts constitutively to maintain endothelial barrier integrity. Tie2, a tyrosine kinase receptor, is found almost exclusively in endothelial cells. (There is no information on whether Angpt/Tie2 signaling is involved in any form of epithelial dysfunction in critical illness.) An increase in pro-inflammatory cytokines in patients with sepsis causes the release of Angpt-2 from storage in Weibel-Palade bodies (WPBs) within endothelial cells (Figure 2) (29). Release of Angpt-2 suppresses Tie2 signaling, reduces Foxo-1 phosphorylation and increases Angpt-2 gene transcription. The loss of Tie2 signaling leads directly to endothelial dysfunction, and in mice its restoration reverses the acute lung injury seen with influenza virus infection (30). Increases in RhoA kinase and myosin light chain kinase activity are other mechanisms
involved in the loss of endothelial barrier integrity and the ensuing plasma leakage (26-29).

In mice (27,28,32) and humans (27-29,31-37), sepsis is associated with increased plasma levels of Angpt-2, increased plasma leakage into the lungs, and increased liver and renal dysfunction (27-33). Tie2 activation maintains or restores endothelial barrier integrity in experimental sepsis (34). In patients with sepsis, an increased serum level of Angpt-2 serves as a useful biomarker that signifies an increased risk of multi-organ failure and death (35-39).

Treatment with statins and ARBs directly affects the Angpt/Tie2 signaling axis. Statins activate Akt and increase phosphorylation of Foxo1, which decreases Angpt-2 production (Figure 2) and increases endothelial barrier integrity (29). Endothelial barrier integrity is also enhanced by statin inhibition of Rho and Rac geranylgeranylation (30).

Moreover, mice with a deletion in vitamin D receptor develop severe LPS-induced acute lung injury, which can be reduced by pretreatment with either an experimental Angpt-2 antagonist or an ARB (40).

ACE2/angiotensin-(1-7)/Mas signaling

Studies published more than a decade ago showed that ACE2 is the functional receptor for SARS coronavirus (41-43). Soon thereafter, ACE2 was shown to protect mice from acute lung injury associated with experimental sepsis (44). This study suggested a broad role for ACE2 signaling in the pathogenesis of sepsis, acute lung injury and other forms of acute critical illness (45-47).

The renin-angiotensin system (RAS) modulates many essential functions that maintain homeostasis. Angiotensin II (Ang II), which acts on type 1 Ang II receptor (AT1R), is central to RAS activities. Ang II increases endothelial barrier permeability (48). The ACE homolog ACE2 acts as a counter-regulator to the activities of Ang II by forming angiotensin-(1-7), which acts via the Mas receptor to oppose the vasoconstrictor and inflammatory effects of ACE/Ang II/AT1R signaling (45-47). ACE2 has been found in alveolar epithelial cells, enterocytes in the small intestines, and endothelial and smooth muscle cells in several organs (43).

| Table 2 Beneficial effects of statin and ARB treatment on endothelial dysfunction |
|---------------------------------|---------------------------------|---------------------------------|
| **Endothelial barrier disruptor/protector** | **Beneficial treatment** | **Endothelial barrier disruptor/protector** | **Beneficial treatment** |
| | Statins | ARBs | Statins | ARBs |
| Angpt-2/Tie2* | Yes | Yes | ROS | Yes | Yes |
| ACE2* | Yes | Yes | eNOS/iNOS | Yes | Yes |
| RhoA/Rac1 GTPase | Yes | Yes | P-selectin/E-selectin | Yes | Yes |
| PAR1/PAR2 | Yes | Yes | TXA2 | Yes | Yes |
| Thrombomodulin | Yes | Yes | PAF | Yes | Yes |
| t-PA | Yes | Yes | Pro-inflammatory cytokines | Yes | Yes |
| PAI-1 | Yes | Yes | MMPs | Yes | Yes |
| VCAM-1/ICAM-1 | Yes | Yes | MPO | Yes | Yes |
| S1P1 | Yes | Nd | C3a, C5a | Yes | Yes |
| VEGF | Yes | Yes | HMGB1 | Yes | Yes |
| VE-cadherin | Yes | Yes | Bradykinin | Yes | Yes |
| Actin cytoskeleton | Yes | Yes | β-arrestin | Nd | Yes |

Endothelial barrier disruptors and protectors (signaling molecules or pathways) are defined according to (7,12). Beneficial treatment is defined as either up regulation or down regulation in cell signaling that improves endothelial barrier integrity (DS Fedson, unpublished observations). ARB, angiotensin receptor blocker; Angpt*, angiopoietin (see text for details); ACE2*, angiotensin converting enzyme-2 (see text for details); PAR, protease activator receptor; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; VCAM-1/ICAM-1, vascular/intercellular adhesion molecule-1; S1P1, sphingosine-1-phosphate-1; VEGF, vascular endothelial growth factor; VE-cadherin, vascular endothelial cadherin; ROS, reactive oxygen species; eNOS/iNOS, endothelial/inducible nitric oxide synthase; P-selectin, platelet selectin; E-selectin, endothelial selectin; TXA2, thromboxane A2; PAF, platelet-activating factor; Pro-inflammatory cytokines, e.g., IL-6, TNF; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; C, complement; HMGB1, high mobility group box 1; Nd, no data.
The ACE2/angiotensin-(1-7)/Mas signaling axis modifies several aspects of both acute and chronic inflammation. It has beneficial effects on insulin metabolism (49) and on the cardiovascular (46,50), renal (51), and coagulation systems (52). It attenuates inflammatory damage to endothelial cells in vascular disease (53-55) and diabetes (56,57). In experimental sepsis, ACE2/ang-(1-7)/Mas signaling down regulates inflammatory changes in endothelial cells (58) and improves outcomes (59,60). Similarly, in experimental acute lung injury, this signaling axis reverses endothelial and epithelial cell dysfunction (61-65) and prevents ARDS (66-68). Children with ARDS have an increase in bronchoalveolar fluid ACE and a decrease in ACE2 (69).

Several experimental studies have demonstrated the benefits of treatments that target ACE2/angiotensin-(1-7)/Mas signaling. In experimental rodent models of sepsis and acute lung injury, ARBs down regulate numerous pro-inflammatory cytokines and improve outcomes (59,62,70). These findings are supported by other studies of ARB treatment in models of cardiac hypertrophy and vascular injury (71-74). Moreover, in a rabbit model of atherosclerosis, statin treatment up regulates ACE2 in the heart, and this is associated with epigenetic histone modifications (75).

**Clinical experience with statin and ARB treatment in patients with critical illness**

The demonstrated effects of statin and ARB treatment on Angpt/Tie2 and ACE2/angiotensin-(1-7)/Mas signaling in endothelial and epithelial cells provide a solid basis for considering using these drugs to treat patients with acute critical illness. Thus far, statins and ARBs have been used to treat patients with sepsis, ARDS, influenza and Ebola virus disease. Opinions vary on the interpretation of published
reports, but on the whole the results have been encouraging.

**Sepsis and pneumonia**

The experimental foundation for treating the host response in patients with sepsis and acute lung injury can be found in studies of simvastatin treatment of LPS-treated mice (76-78). There have been more than 25 observational studies of outpatient statin treatment in patients hospitalized with infection, pneumonia or sepsis (79). Overall, statins were found to reduce episodes of hospitalization and mortality, although a high degree of heterogeneity among the studies has led to caution in interpreting the results.

Four reports of randomized controlled trials (RCTs) of inpatient statin treatment of ICU patients with sepsis and ARDS have been published (80-85). In three of these reports, patients were mechanically ventilated. None of the RCTs showed a reduction in mortality, and three trials were abandoned early for reasons of futility. Statin treatment was found to be safe in these ICU patients, but it was probably “too little too late”; in one study, patients had been treated with mechanical ventilation for a mean of eight days before statin treatment was begun (81).

Another RCT of statin treatment in sepsis patients was conducted by clinicians in Birmingham, UK (86), although their study has received little attention from intensive care specialists. Patients who presented to the emergency department with signs of sepsis but no evidence (yet) of multi-organ failure were randomized to receive either atorvastatin (49 patients; 40 mg per day) or placebo (51 patients). All study subjects had been statin-naive for at least two weeks, and treatment was started as soon as they were hospitalized. The primary goal was to determine whether “statin treatment might reduce the absolute rate with which sepsis converted to severe sepsis” (i.e., multi-organ failure) (86). The investigators calculated they would need 414 patients to detect a statistically significant reduction in severe sepsis of 15% (e.g., from 40% to 25%). Although slow recruitment forced the investigators to stop their trial prematurely, they succeeded in achieving their primary goal: the occurrence of severe sepsis was reduced not by 15% as planned, but by 83%. Because the development of multi-organ failure in sepsis patients is thought to be due to the loss of endothelial barrier integrity, it is reasonable to conclude that the positive outcome in this RCT reflected the activity of atorvastatin in maintaining endothelial barrier integrity. As discussed above, statins probably contribute to maintaining endothelial barrier integrity by affecting the Angpt/Tie2 signaling axis (30).

**Influenza**

The host response to influenza virus infection has been studied extensively, and many of these studies have been recently reviewed (87-92). In both experimental and human influenza, a greater degree of virus replication is generally associated with greater inflammation and more severe disease (93,94). However, individual influenza viruses may differ in the extent to which they elicit inflammatory responses, and the degree of hypercytokinemia is not always directly associated with levels of virus replication or mortality (88,95).

Endothelial and epithelial cells are intimately involved in the host response to influenza virus infection, and it is often difficult to separate the two. Both cell types can be infected *in vitro* with influenza A H5N1 viruses (96-98), and this is associated with a brisk and unbalanced inflammatory response involving (among other things) NF-kappa B and interferon regulatory factor (IRF) 3 (99,100). Studies in cell co-culture systems, however, show that influenza viruses primarily target epithelial rather than endothelial cells (97,101,102). Nonetheless, while helpful, these *in vitro* studies cannot take account of the complex interplay between these cells and other components of the host response *in vivo* (especially leukocytes and macrophages), which contribute to the inflammatory response (102-106). Tellingly, the importance of host factors, not virus replication, was shown conclusively in a study of experimental acute lung injury following intra-tracheal instillation of inactivated H5N1 influenza virus (107).

In the lung, ACE2 is found primarily in epithelial cells (108), and the ACE2/angiotensin-(1-7)/Mas axis directly regulates epithelial cell survival (109,110). In mice, ACE2 is a mediator of the acute lung injury caused by influenza A H5N1- and H7N9-virus infection (111,112), and in patients, increased ACE2 levels are associated with severe disease (111,113). In mice experimentally infected with H5N1 influenza, treatment with an ARB (losartan) improves survival (114).

The Angpt/Tie2 signaling axis is also involved in the pathogenesis of experimental influenza (32). Angpt-like 4, a member of the Angpt family that does not signal through Tie2, also promotes vascular permeability in experimental influenza (115). Importantly, a specific Tie2 agonist (Vasculotide) promotes survival in mice infected with influenza virus (31). In this study, all of the mice that were
given only an antiviral agent immediately after infection died, whereas those that were also given a Tie2 agonist starting as late as five days after infection survived.

Statins reduce influenza virus replication in vitro (116), but for several reasons, studies of statin treatment of influenza virus-infected mice have been inconclusive (117). There is still a good possibility that statins might contribute to improved survival in human influenza because, among other things, they downregulate pro-inflammatory cytokines. Statins probably act in other ways as well. For example, in mice, TNF-related apoptosis-inducing ligand (TRAIL) signaling promotes apoptosis in epithelial cells (118), while in humans with acute coronary syndrome (another inflammatory illness), statins reduce endothelial cell apoptosis (119). Thus, statins would probably have a positive effect on the host response to influenza. In all of these studies, statins were used by themselves, and not combined with other immunomodulatory agents.

More than a decade ago, when the prospect of a global avian H5N1 influenza pandemic was of great concern, it was suggested that treating the host response might be an effective way to mitigate pandemic mortality (120-122). The need for such an approach was amply demonstrated during the influenza H1N1 pandemic in 2009-2010, when more than 90% of the world’s people had no access to adequate supplies of pandemic vaccines and antiviral agents (121,122). More recently, the emergence of the influenza A H7N9 and similar influenza viruses has served as a reminder that the pandemic threat has not disappeared (123). There are many ongoing efforts to improve the global supply of influenza vaccines (124-126). Nonetheless, during the first 6 months of the next pandemic, access to pandemic vaccines will be severely limited for virtually everyone in the world (121,122).

Influenza accounts for a substantial proportion of cases of medically attended acute respiratory infection (MAARI). Two large observational studies of statin treatment in MAARI patients have yielded conflicting results (there are no such studies for ARBs). In one study from the UK, statin treatment resulted in a 33–35% reduction in 30-day all-cause mortality (127), although the proportion of these illnesses that were caused by influenza virus infection was unknown and the investigators were unable to control for previous influenza vaccination in their analysis. In another study from the US, the effectiveness of influenza vaccination in MAARI patients was actually reduced in individuals who were taking statins (128), although like the UK study, the proportion of illnesses caused by influenza virus infection was unknown. Nonetheless, these findings from the US are compatible with those of another study, which showed that elderly patients taking statins had reduced antibody responses following influenza vaccination (129).

In a recent report, investigators used a test-negative design to study the effectiveness of influenza vaccination, outpatient statin treatment, or both in preventing laboratory-confirmed, medically attended influenza in adults ≥45 years in age (130). Table 3 summarizes their findings for influenza A H3N2. (Similar findings were reported for influenza A H1N1 and influenza B, although the numbers of such patients were small.) In patients who had received influenza vaccine, outpatient treatment with statins reduced the effectiveness of vaccination from 46% to 25%. However, in unvaccinated subjects, outpatient statin treatment alone reduced the number of cases of influenza by 37%. When influenza vaccines are unavailable, as will occur during the early months of the next pandemic, this finding will take on special meaning.

Interpretation of the results of outpatient studies of statin treatment in patients with MAARI and laboratory-confirmed influenza may be debatable, but it is more important to know...
whether statins benefit patients hospitalized with laboratory-confirmed influenza because it is hospitalized patients who are at increased risk of dying (121). Two observational studies suggest that inpatient statin treatment could reduce 30-day all-cause mortality (Table 4) (131,132). Both studies were conducted using the same database, both used propensity scoring and both controlled for age, sex, underlying co-morbid conditions, and (importantly) previous influenza vaccination and antiviral treatment. The first study (retrospective cohort) found that statin treatment reduced 30-day all-cause mortality by 41%, suggesting that statins might be useful in treating influenza patients requiring hospitalization (Table 4) (131). The second study (case-control) found that statins reduced 30-day mortality by an even greater margin −59% (Table 4) (132). Nonetheless, investigators for the second study concluded that because of unmeasured confounding, statins should not be used “as adjunct treatment for preventing death among persons hospitalized for influenza” (132). The findings for statins and ARB treatment of community-acquired pneumonia (Table 1) and those for statin treatment of laboratory-confirmed influenza (Table 3) suggest this conclusion is premature.

**Ebola virus disease**

More than a decade ago, Ebola scientists noted clinical similarities between Ebola and septic shock (133). When the outbreak of Ebola virus disease appeared in West Africa in 2014, experience with treating the host response in patients with sepsis, pneumonia and influenza suggested the same approach might improve outcomes in Ebola patients.

Recent experimental studies suggest that statins might be effective against the Ebola virus itself. For example, heme-oxygenase-1 (HO-1) has been shown to suppress Ebola virus replication (134), and statins are known to up regulate HO-1 (135). Moreover, Ebola viruses are cytotoxic because they target cell membrane cholesterol (136), which is affected by statins. Other studies, however, suggest that the host response to Ebola virus infection itself could be a target of treatment. Genetic studies of Ebola in mice have shown that endothelial dysfunction and increased vascular permeability are associated with Tie2 (137). Ebola virus glycoprotein activates endothelial cells in vitro via a TLR4-mediated mechanism (138), and TLR4 is down regulated by statin treatment. Most of these experimental findings were published before Ebola virus-infected health care workers were evacuated to the US and Europe. Clinical findings documented in the case reports for these patients convincingly demonstrated endothelial dysfunction and massive fluid losses that reflected a breakdown of endothelial barrier integrity (139,140).

On August 15, 2014, shortly after WHO declared Ebola to be a Public Health Emergency of International Concern, a letter was published online suggesting that statins and/or ARBs might be useful in treating Ebola patients and should be tested (141). This idea was not well received by Ebola scientists (142) and officials at the World Health Organization (WHO) (DS Fedson, unpublished observations). Nonetheless, a few months later, physicians in Sierra Leone were able to treat consecutively approximately 100 Ebola patients with a combination of atorvastatin (40 mg/day) and irbesartan (150 mg/day) (143,144). Some of these patients were also treated for 2–3 days with clomiphene, a selective estrogen receptor modifier (SERM) previously shown to have antiviral activity against Ebola virus (145,146). [Although clomiphene has not been described as having immunomodulatory activities, other drugs in the same category have been used to treated immune-mediated diseases (147)]. There was no financial or logistical support for a proper clinical trial, but thanks to a private donation the drugs were made available to local physicians. Only three inadequately treated patients are known to have died (143,144). The physicians and

<table>
<thead>
<tr>
<th>Study (references)</th>
<th>Method</th>
<th>No. of subjects cases/controls</th>
<th>Adjusted OR/HR (95% CI)</th>
<th>Reduction in 30-day all-cause mortality (%)</th>
</tr>
</thead>
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<tr>
<td>Vandermeer et al. (131)</td>
<td>Retrospective cohort</td>
<td>1,030/2,013</td>
<td>OR =0.59 (0.38–0.92)</td>
<td>41</td>
</tr>
<tr>
<td>Laidler et al. (132)</td>
<td>Case control</td>
<td>670/670</td>
<td>HR =0.41 (0.25–0.68)</td>
<td>59</td>
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The two studies were performed using the same database. Both used propensity scoring and the analyses adjusted for age, sex, underlying high-risk conditions and previous influenza vaccination and antiviral treatment. OR, odds ratio; HR, hazard ratio; CI, confidence interval.
supervising health officials responsible for these patients refused to publicly release information on their experience, but their treatment results were documented immediately in letters and memoranda (Figure 3) and eventually in local newspapers (148). Unfortunately, international organizations involved in the Ebola response, including WHO, have made no effort to validate these findings (DS Fedson, unpublished observations).

Earlier, in September 2014, health officials at WHO decided that only investigational treatments that target the virus would be tested in Ebola patients (149) (experimental Ebola vaccines were also approved for testing). Several clinical trials were undertaken (at great expense) to test experimental antiviral drugs, convalescent plasma and monoclonal antibodies (150). Because of a decline in the number of cases, some of the trials had to be abandoned. In the few that were completed, none of the treatments had a major effect in improving overall survival in Ebola patients, especially in those with high virus loads; i.e., those most in need of effective treatment (151-154).

In spite of these disappointing clinical experiences, Ebola scientists continue to focus on developing treatments that target the virus (155,156). Some investigators insist that the rhesus macaque non-human primate (NHP) model provides the “gold standard” for testing investigational Ebola treatments (157). Surprisingly, no investigator has ever shown that Ebola virus infection in NHPs replicates the endothelial dysfunction and massive fluid losses that are the hallmark of human Ebola virus disease. This contrasts with the experience of earlier investigators who showed that NHPs could be used to study endothelial dysfunction in other models of critical illness (158-160). Moreover, Ebola scientists seem to be unfamiliar with the findings of HIV scientists who have studied simian immunodeficiency virus (SIV) infection in two NHP species. Clinical outcomes are very different in rhesus macaques, all of whom die, compared with sooty mangabeys, all of whom live (161,162). Remarkably, both species have similarly high virus loads. The findings from SIV infection in these two NHP models demonstrate convincingly that the host response, not virus
load, primarily determines outcome.

Investigators have yet to explain why gastrointestinal endothelial dysfunction is so prominent in Ebola virus disease, whereas the lung, liver and kidneys are the primary targets of severe or fatal sepsis, pneumonia and influenza. [Interestingly, influenza viruses naturally cause gastrointestinal infection in waterfowl, and experimental GI infection of cats shows that influenza A H5N1 virus targets intestinal endothelial cells and leads to widespread systemic infection (163)]. The complex relationship between the gut and other organs in critical illness has only begun to be explored (164). Experimental and human studies show that ACE2 in gut epithelial cells is necessary for normal absorption of amino acids (165,166) and glucose (167). In addition, the absence of ACE2 in gut epithelial cells alters immunity and leads to increased inflammation (165). Both experimental animals (168) and humans (169) with acute intestinal inflammation have elevated plasma levels of ACE2 and angiotensin-(1-7). In animal models of acute intestinal inflammation, treatment with ARBs down regulates pro-inflammatory cytokines and reduces oxidative stress and epithelial apoptosis (170-172), and statins have similar effects (173-175). Apoptosis of intestinal epithelial cells is a common finding in human and animal studies of critical illness (164). It is tempting to speculate that the response of Ebola patients in Sierra Leone to combination statin/ARB treatment might have been due to the favorable effects of ARBs (and perhaps statins) on ACE2 in intestinal epithelial (and perhaps endothelial) cells.

Clinical investigators continue to seek a better understanding of the host response to Ebola virus infection. A recent study of seven Ebola virus-infected healthcare workers explored 54 separate plasma biomarkers of severe disease (176). The investigators documented activation of the coagulation cascade and evidence of endothelial dysfunction, although levels of Angpt-2, ACE2 and angiotensin-(1-7) were not measured. These biomarker findings reflect the increase in vascular permeability that clinicians have long known to be a central feature of Ebola virus disease.

A few investigators believe that treating the host response in Ebola patients is a reasonable idea (177,178), but their views are not widely shared. Recently, other investigators reviewed the overall clinical experience in managing patients with Ebola virus disease in and outside of West Africa (179). They noted that open-label, uncontrolled studies like the statins/ARB experience in Sierra Leone (143) “precluded any conclusions” about the effectiveness of this treatment. Because no specific treatment had yet been shown to be effective, they concluded, “improving the global capacity to provide supportive critical care... may be associated with the greatest opportunity to improve patient outcomes” (179). They offered no suggestions on how or at what cost this could be accomplished.

**Implications for treating the host response to other emerging virus infections**

The threat of a major influenza pandemic has not disappeared. Virologists regularly document the natural emergence of influenza virus reassortants with pandemic potential (180). According to WHO, several other emerging viruses also threaten to cause epidemics or pandemics, and urgent attention should be given to developing vaccines and treatments (Table 5) (181). In practical terms, it is unlikely that specific vaccines will be developed for each of these viruses, let alone produced, distributed and administered to populations before one of these viruses emerges. The same is true for specific antiviral agents. Yet the diseases associated with all but one of the emerging viruses requiring urgent research and development (R&D) are characterized by endothelial dysfunction (there are no data for Rift Valley fever) (42,182-185). Endothelial dysfunction is also seen in

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**Table 5** Emerging virus diseases likely to cause major epidemics or pandemics (181)

<table>
<thead>
<tr>
<th>R&amp;D requirements</th>
<th>Emerging viruses and other pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Require urgent R&amp;D</td>
<td>Ebola, Marburg, Lassa fever, Crimean Congo hemorrhagic fever, MERS and SARS coronaviruses, Nipah, Rift Valley fever</td>
</tr>
<tr>
<td>Require R&amp;D as soon as possible</td>
<td>Zika, chikungunya</td>
</tr>
<tr>
<td>R&amp;D pipeline already exists</td>
<td>HIV/ADIS, tuberculosis, malaria, avian influenza, dengue</td>
</tr>
</tbody>
</table>

R&D, research and development.
dengue and Hantavirus pulmonary syndrome (186), and it is a feature of several diseases thought to represent bioterrorist threats, including inhalation anthrax (32,187).

As discussed earlier, a large number of agents that appeared promising in experimental studies have not been found to be effective in clinical trials (2). The recent failure of RCTs of statin treatment to improve outcomes in mechanically ventilated sepsis patients (85) has caused many observers to abandon hope that statins will be effective in treating any form of acute critical illness. In the absence of clinical trial evidence showing that treating the host response actually works, these experiences remind us to remain cautious. The failure of corticosteroid treatment to reduce mortality in patients with severe influenza is well known (188). A recent RCT of statins in adults with dengue was unsuccessful (189). A trial of a TLR4 antagonist failed in patients with severe sepsis (190,191). An exploratory RCT of aspirin treatment of patients at risk of developing ARDS was abandoned because treatment was ineffective (192,193). Several factors could explain why these trial results were disappointing, including a low level of severe disease and mortality in the patient populations being studied (189). In addition, most of these trials were based on earlier experimental or observational studies that examined single agent treatment. Thus, another reason for their failure might be that none of them studied combination treatment with more than one drug.

Treatments that target the infecting virus often bring modest benefits at best, as shown by the clinical trials in Ebola patients discussed above. A study of neuraminidase inhibitors in patients hospitalized during the influenza A H1N1 pandemic reduced overall hospital mortality by 19%, although mortality was reduced by approximately 50% in those who were treated within 2 days of symptom onset, something difficult to achieve in routine clinical care (194). By comparison, numerous experimental studies have shown that modifying the host response (e.g., cytokine knock-out) can dramatically improve survival without having any effect on virus load (121).

Treating the host response with drugs that target endothelial (and perhaps epithelial) dysfunction represents an alternative and potentially more effective strategy for managing a wide variety of emerging virus diseases (195). There is a good chance that a small number of inexpensive, generically produced and widely available drugs that modify common features of the host response to each of these viruses could be used in the syndromic treatment of them all (121,122,143,144).

**Implications for treating the host response to other acute infectious diseases**

Observational studies suggest that treating the host response improves outcomes in patients hospitalized with sepsis, pneumonia and influenza, as discussed above. Because the host response to these diseases involves similar or overlapping mechanisms related to endothelial dysfunction, these findings suggest that in addition to treating emerging virus diseases, drugs like statins and ARBs might be used to treat patients with other, acute “everyday” infectious diseases in which similar mechanisms are involved. Some of these diseases occur only occasionally [e.g., Hantavirus pulmonary syndrome (15,186) or inhalation anthrax (187)], but others are far more common, especially in low-income countries. One of them is malaria.

Clinical studies of severe and cerebral malaria (both falciparum and vivax) in children and adults treated with antimalarial drugs have documented endothelial dysfunction: decreased plasma levels of angpt-1, increased levels of angpt-2 and increased angpt-2/angpt-1 ratios (196-203). Other findings include elevated levels of several pro-inflammatory cytokines and chemokines and other biomarkers indicating endothelial [vascular/intercellular adhesion molecule-1 (VCAM-1/ICAM-1), endothelial selectin (E-selectin)], coagulation (thrombomodulin) and complement (C5a) activation.

In experimental studies of cerebral malaria, mice infected with *Plasmodium berhei* ANKA develop neurological signs five to six days after infection. At the same time, signs of inflammation (increased pro-inflammatory cytokines and chemokines) and endothelial dysregulation become prominent. Under conditions where antimalarial treatment only partially reverses the course of illness, additional treatment with a statin (204-206) or another intervention (207,208) that affects endothelial cells reduces neuro-inflammation, restores endothelial barrier integrity, and increases survival. Dysregulation of the Angpt/Tie2 signaling axis is also seen in experimental *P. berghei* infection (32,209-211). Treatment with an antimalarial drug combined with either angpoeitin-1 (210) or an ARB (irbesartan) (211) restores endothelial barrier integrity and improves survival.

These clinical and experimental finding suggest that adjunctive treatments targeting endothelial dysfunction might improve outcomes in patients with severe and cerebral malaria (198,199). Earlier studies had shown that decreased endothelial nitric oxide (NO) was associated with severe and fatal malaria, but a recent RCT of inhaled NO
in malaria patients showed no effect on plasma levels of angpt-2, parasitemia or mortality (212). Given the response of Ebola patients to statin/ARB treatment discussed above, this combination should be considered for inclusion in a clinical trial of adjunctive treatment in malaria patients.

Two additional observations in malaria patients may be relevant for Ebola treatment. First, endothelial dysfunction and systemic inflammation persist for many weeks after antimalarial treatment has cleared the circulation of parasitized red blood cells, and similar findings have been seen following non-malarial infections (213). These observations suggest that persistent endothelial dysfunction might contribute to post-Ebola syndrome and could be a target for treatment.

Second, in a large study of Ebola patients, all of whom received antimalarial treatment with artemether-lumefantrine, the presence of parasitemia was associated with a significant 20% increase in survival (214). This finding was independent of age and Ebola virus load, and the highest level of parasitemia was associated with an 83% survival rate. Several explanations for this “remarkable phenomenon” were suggested, including early up regulation of IFN-β, induction of NK cells, and dampening of the Ebola virus-induced cytokine storm (214). In an earlier study of Ebola patients, all of whom were given antimalarial treatment; those who were treated with artesunate-amosiaquine had a 31% lower risk of mortality compared with those treated with artemether-lumefantrine (215). However, in mice infected with a mouse-adapted Ebola virus, treatment with all four antimalarials, either alone or in combination, had no effect on survival (214), indicating the drugs had no direct antiviral effect. Interestingly, artesunate is known to have broad immunomodulatory activities against microbial infections and inflammatory disorders. In a study of cerebral malaria in P. berghei-infected mice, artesunate (but not mefloquine) improved survival by a mechanism that was independent of its antimalarial activity (216). In studies using murine VE cells, artesunate (I) inhibited NF-kappa B translocation to the nucleus; (II) down regulated the expression of ICAM-1; and (III) prevented parasitized red blood cells from attaching to endothelial cells. Taken together, these observations suggest that in Ebola patients, pre-existing malaria parasitemia might have provided a measure of protection against the effects of Ebola virus on endothelial barrier integrity by activating endothelial defence mechanisms (e.g., up regulating angpt-1 and down regulating angpt-2). Artesunate treatment itself might have had an additional, independent effect on endothelial barrier integrity. These mechanisms are plausible in light of the response of Ebola patients to statin/ARB treatment, a regimen that affects the Angpt/Tie2 signaling axis and improves endothelial barrier integrity.

**Ebola and “lessons learned”**

In evaluating the response to the H1N1 influenza pandemic in 2009, a WHO report concluded, “The world is ill prepared to respond to a severe influenza pandemic or to any similar global, sustained and threatening public health emergency” (217). The response to the Ebola outbreak in West Africa five years later showed that little had changed (218).

Many commentaries have examined the shortcomings of the international Ebola response, especially the response by WHO (e.g., 219,220). Four independent “lessons learned” reports have offered overlapping recommendations on how to structure a better WHO and international response for managing future epidemics and pandemics (221-224), and published summaries highlight their common features (225,226). Each report recommends strengthening national health systems and reorganizing and improving WHO’s governance and capacity to respond to emergencies. All of them recommend that WHO establish an independent Center for Emergency Preparedness and Response and create a contingency fund to support the rapid deployment of emergency response capabilities (225). They also emphasize the importance of system-wide accountability (e.g., WHO, the United Nations and The World Bank) to ensure an effective global response to future health emergencies.

The four “lessons learned” reports also offer several recommendations for accelerating R&D, and in each report WHO is expected to play a major role (225). WHO has developed its own R&D Blueprint that aims to “reduce the time between the declaration of an international public health emergency and the availability of effective tests, vaccines, antivirals and other treatments...” (227). This R&D Blueprint will serve as “a convening mechanism for public health officials, scientists, and product developers, and an instrument to articulate technical guidance for R&D preparedness and response” (227). In doing so, WHO hopes to fulfill its “global mandate to set evidence-based priorities and standards for research, ensuring that all voices are heard and avoiding conflicts of interest” (227).

The most detailed recommendations for R&D can
be found in the report of the Commission on a Global Health Risk Framework for the Future (223). The GHRF Commission calls for establishing a Pandemic Product Development Committee (PPDC) that will be accountable to a Technical Governing Board under the supervision of WHO and its Director-General. The PPDC would seek the participation of national regulatory authorities, industry, research organizations, and other public and private stakeholders to promote regulatory convergence, pre-approve clinical trial designs, manage intellectual property and product liability, and expedite the manufacturing and distribution of vaccines, treatments and diagnostics. Adequate funding for this enterprise will be essential, and might require establishing a new global financing mechanism for innovation (228). Two reports suggest this effort would cost at least $1 billion per year (223-225).

None of the Ebola “lessons learned” reports mentions the statins/ARB experience in Sierra Leone and what it might mean for clinical trials of treatments that target the host response (218-230). Instead, the reports call for R&D on new treatments that seem to focus exclusively on new, experimental agents that target only the virus and will undoubtedly require extensive investment (221,223-225). Moreover, the recommendations for coordinating this research call for a prominent role for WHO, which firmly rejected the idea of studying treatments that target the host response to Ebola and which has never convened a meeting to provide “technical guidance for R&D preparedness and response” that includes treating the host response (122,149,227; DS Fedson, unpublished observations). Not surprisingly, WHO has realistically concluded “most individual funding agencies are likely to make decisions on a case by case basis, in line with their mandates and mission” (227).

Several Ebola experts have objected to the publication of reports describing the treatment experience in Sierra Leone (143,144), saying these reports do not constitute evidence of protection (DS Fedson, unpublished observations). These critics have not explained why they have opposed undertaking clinical trials to obtain the data they now demand, or why they have shown no interest in validating what reportedly happened to Ebola patients who were treated in Sierra Leone.

Clinical trials of new treatments
Testing new treatments in the midst of a severe outbreak is fraught with difficulty. The clinical trials that were undertaken during the Ebola outbreak required large-scale international collaboration and were very expensive (151-153,229). One notable development was expansion of the activities of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) (229,230). ISARIC developed a set of pre-approved and adaptable syndrome-based protocols for clinical research and clinical trials that are available online to its member networks in Africa and beyond. ISARIC and its affiliated Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) have developed relationships with funders and other organizations that support training and capacity development (230). These developments address many of the administrative, regulatory, legal and ethical difficulties that could otherwise impede a rapid research response during future outbreaks.

When testing new treatments in the setting of an Ebola-like outbreak, a classical 1:1 RCT will seldom be appropriate or even feasible, so choosing an alternative trial design becomes vitally important. As noted recently, “While the scientific merits of RCTs are powerful, advocates for them have not paid enough attention to competing factors that shape research ethics, such as the need for clinical equipoise in starting an RCT, the weakness of knowledge gained when small sample sizes prevail and available supportive care is given to all, the importance of rapidly finding what agent is best among competitors rather than insisting on starting from scratch as RCTs do, and retaining community trust in participating in any RCT with a control arm. Addressing these concerns is crucially important if any trials are to succeed in very challenging circumstances” (231). All of these issues became evident during the recent Ebola clinical trials.

During the Ebola outbreak, a consensus emerged in favor of adaptive trial designs that would minimize the number of patients who would receive less than effective treatment and at the same time accelerate the discovery of one or more treatments that would best improve patient survival (232-234). The statins/ARB treatment experience in Sierra Leone suggests, however, that an adaptive trial design might not be needed. Historical observations show that the effects of many treatments can be so dramatic that bias can be ruled out (235); in these instances, “the observations speak for themselves” (236). The question that must then be asked is “how much difference between treatment outcome and the natural outcome is enough?” (236). Simulation studies show that “implausibly large associations, both between treatment and confounding factor and between confounding factor and outcome, are generally required to explain risks
beyond relative rates of 5–10”, and “rate ratios beyond 10 are highly likely to reflect real treatment effects” (236). Compared with historical controls, survival rates in Ebola patients treated with the statin/ARB combination were of this order of magnitude (143,144). Thus, it could be argued that in a future outbreak of Ebola (or Ebola-like disease), an adaptive design clinical trial of a statin/ARB-like treatment regimen might not be needed.

If nothing else, the experience in Sierra Leone suggests that the clinical equipoise needed to justify a RCT of a treatment targeting the host response to Ebola virus infection may no longer exist. Moreover, RCTs “bring final quantification, (but) they offer little scientific novelty in themselves. Before an idea can be confirmed or quantified, it has first to be discovered. For true intellectual advancement, i.e., in proposing new problems, new solutions, or new ideas... (it is case reports and case series that suggest)... mechanisms (and) therapeutic surprises” (237). The case series of Ebola patients who were treated with a statin/ARB combination constitutes such a surprise.

**Suggestions for treatment research**

There is an obvious need for effective drugs to treat each of the emerging virus diseases that threaten to cause epidemics or pandemics. Important lessons have been learned from studies of treatments for influenza, sepsis, pneumonia and Ebola, as discussed above. Most of these studies have been observational in design, which means that compared with RCTs they have well recognized limitations (e.g., healthy user bias, confounding by indication and other unmeasured confounding variables) (238-240). Nonetheless, physicians know that “nearly all clinical decisions involve probabilistic reasoning, ...so a realistic goal for observational research may not be the high standard set by RCTs but instead the level of certainty needed to influence a ... treatment decision” (240). This admonition is especially important given the short time frame (a few weeks at most) for studies that evaluate treatment outcomes in acute critical illness.

**Ebola follow up and post-Ebola syndrome**

A recurrence of acute Ebola virus disease is still possible, and plans should be made for clinical studies of experimental and generic treatments if this occurs. In the meantime, the statin/ARB treatment experience in Sierra Leone should be evaluated and the findings independently validated (143,144). If validated, a conventional clinical trial of statin/ARB treatment might not be necessary (see discussion above).

The dimensions of post-Ebola syndrome also need to be defined: the duration of virus persistence and the long-term effects of uveitis, arthritis, and neurologic complications (241). Several follow up studies to do this are now underway. Although it is unclear whether antiviral agents will be needed to clear the virus, investigators should not overlook the possibility that statins, ARBs and drugs like clomiphene could be useful in treating the post-Ebola complications seen in these patients (242-245). Investigators should also consider the possibility that post-Ebola syndrome might share features in common with chronic critical illness due to other causes (246).

**Cellular mechanisms that support virus replication**

In clinical studies, treatments that target the virus have been only modestly effective, yet antiviral treatments are still the focus of new research strategies, including drug repurposing (247). If new antivirals must be specific for each individual virus, this approach to research has many disadvantages. One way to overcome this problem might be to discover drugs that target common cellular mechanisms that support virus replication. As proposed for influenza viruses (248), this approach would minimize the possibility of virus resistance, would (presumably) work only in virus-infected cells (see below), would likely reduce unwanted side effects, and could include several drugs that are already licensed for treating other diseases. Suggested cellular targets for influenza antiviral intervention include (I) the Raf/MEK/ERK kinase and p38 MAPK kinase pathways and (II) the IKK/NF-kappaB pathway. Cell culture studies of several unlicensed agents that down regulate these pathways have given promising results (248). Interestingly, there is considerable molecular cross-talk between these two pathways in endothelial cells (249), epithelial cells (250), and macrophages (251). In each of these cells and in rat kidneys *in vivo* (252), statins down regulate both of these pathways. Statins also prevent Ang II-induced endothelial dysfunction by inhibiting p38 MAPK (253,254). In addition, ARBs inhibit the RAF/MEK/ERK and p38 MAPK pathways (255-257). Finally, in septic mice, giving an ARB 30 minutes after cecal ligation and puncture inhibited NF-kappaB, p38 MAPK and ERK1/2, reduced levels of pro-inflammatory cytokines in lung tissue, and significantly improved survival (258). Considered together, these findings suggest that in influenza and perhaps other emerging virus diseases,
Biomarker studies

An important discussion is taking place among critical care investigators regarding the utility of biomarkers in guiding their studies. This discussion has been prompted by (I) the failure of clinical trials in sepsis and ARDS to identify new treatments that will improve patient outcomes (2); and (II) the availability of several new laboratory and computational technologies that allow investigators to identify an increasingly large number of biomarkers that might inform their clinical studies.

Investigators recognize there is substantial variation in the host response to critical illness. To address this heterogeneity, one group of investigators believes that by using the techniques of integrated genomics (e.g., mapping gene expression as expression quantitative trait loci) they can define “subgroups of patients with different immune response states and prognosis ... (that will provide) ... new insights into the pathogenesis of sepsis and create opportunities for ... precision medicine ... to target therapeutic inventions and improve sepsis outcomes” (259). These techniques can be used to define patient subgroups that show greater immunosuppression and higher mortality. They are also said to be more precise than definitions based on clinical criteria alone.

Another group of investigators has taken up the challenge of “rethinking strategies” for clinical trial design by contrasting “lumpers” and “splitters” (260). Lumpers assemble heterogeneous groups of patients using simple syndromic definitions, but they are unable to identify subgroups within trial populations that have specific dysregulation of immune pathways or poorer outcomes. By contrast, splitters are interested in identifying specific subtypes in order to “match the right treatment to the right patients” (260). To address these conflicting views, the investigators propose three strategies to improve clinical trial design: practical enrichment (i.e., decrease “noise” in clinical trials), prognostic enrichment (i.e., identify subgroups at higher risk) and predictive enrichment (i.e., identify patients who will respond best to treatment). They believe that “different treatments require different target populations” (260). Because these populations cannot be identified beforehand, they argue that high-throughput searches can be used to identify biomarkers of therapeutic responsiveness that could inform clinical trial design. They believe that “tightly defined criteria enriching for treatment benefit will be the key to advancing treatment for sepsis and ARDS”, and advocate moving beyond a “one-size-fits-all” approach to treatment research (260).

Although the discussion of the role of biomarkers summarized above is thoughtful, it is important to ask whether treatment advances that require “greater personalization of care” (260) will be relevant to discovering new ways to treat patients with emerging virus diseases. To be useful, tests for biomarkers must be rapid, highly accurate and inexpensive. Furthermore, investigators must not overlook “evidence-based treatments that are broadly applicable”, and recognize that “substantial investments into disease subtyping have not always translated in effective targeted treatments” (260). In all likelihood, many if not most emerging virus diseases will first (or eventually) affect people in low- and middle-income countries. It is not clear whether an approach to treatment discovery that is based on “precision” or “personalized” medicine will in any practical sense meet their needs.

A different approach to treatment research

The search for ways to treat patients with Ebola virus disease is still dominated by a focus on drugs that target the virus (261,262). The Ebola “lessons learned” reports call for huge investments that (it is hoped) will lead to the discovery of novel therapeutic agents (223-225). The reports call for this research to be coordinated at an international level, with active leadership by WHO. Given the failures outlined in the “lessons learned” reports and the disappointing results from clinical trials of investigational treatments in West Africa (150-154), it is important to ask what should be done when “underperforming big ideas in research become entrenched” (263).

The ideas of “precision” or “personalized” medicine and the technologies on which they are based have become central to the research of many scientists, and they are widely accepted by institutions that support their work. Yet, for all of their complexity and promise, systems biology and personalized medicine have significant intellectual limitations (264-266). Enormous waste has been documented in biomedical (267) and clinical (268) research. Moreover, introducing a new scientific idea can be difficult (269): just ask an investigator who has prepared
cell function (275,276). Statins and ARBs have broad and systemic and cellular metabolism and how it affects immune immunometabolism: the study of the relationship between diseases and that has received increasing attention is widespread and complex. The effects of statin and ARB treatment on the host response are the diseases themselves are systemic in nature, and the have been a principal focus of much of this research (273,274), pathways common to these and other diseases caused by (I) two inexpensive and widely available generic drugs like statins and ARBs; (II) the shared mechanisms for the pathophysiology of these diseases; (II) laboratory evidence of how these treatments work; and (III) observations of physicians and clinical epidemiologists showing that these treatments work in patients with several types of critical illness.

The relevance of this approach for treating patients who in the future might become infected with an emerging virus is based on existing knowledge of pathophysiological mechanisms shared by all of these viruses and how these mechanisms are affected by treatment (272). More specifically, the studies reviewed here focus on (I) the cellular targets of several forms of critical disease (endothelial and epithelial cells); (II) the shared mechanisms of molecular dysfunction found in these diseases (the Angpt/Tie2 and ACE2/angiotensin-(1-7)/Mas signaling axes); and (III) two inexpensive and widely available generic drugs (statins and ARBs) that target the dysfunctional signaling pathways common to these and other diseases caused by emerging viruses. Although endothelial dysfunction has been a principal focus of much of this research (273,274), the diseases themselves are systemic in nature, and the effects of statin and ARB treatment on the host response are widespread and complex.

One area of research that is relevant to all of these diseases and that has received increasing attention is immunometabolism: the study of the relationship between systemic and cellular metabolism and how it affects immune cell function (275,276). Statins and ARBs have broad and well-known anti-inflammatory and immunomodulatory activities (5,6), but they also affect immunometabolic pathways. For example, oxidative phosphorylation and fatty acid oxidation are characteristic of M2 macrophages (276). Statins and ARBs reduce oxidative stress (277), ARBs promote fatty acid oxidation (278), and both are associated with M2 macrophage phenotypes (279,280). Statins affect T cell polarization by favoring T regulatory cells over Th17 cells (276,281). In addition, AMP-activated protein kinase (AMPK) acts as a master regulator of cellular energy balance by maintaining glucose and lipid homeostasis (275). AMPK is up regulated by statins (282) and ARBs (278). These are just a few of the many ways that statins and ARBs affect immunometabolic pathways.

Conclusions

The Ebola experience in West Africa is a reminder of the ongoing threat of emerging viruses that could cause severe epidemics or pandemics. The international response to the Ebola crisis has been widely criticized, not least for the earlier failure to develop vaccines and treatments that could have mitigated its devastating impact. The reasons for this failure are understandable: an outbreak of this magnitude was historically unprecedented, Ebola vaccines and treatments were perceived as having no commercial value, and other ongoing problems (e.g., malaria, HIV/AIDS) demanded attention.

The international response to the Ebola crisis, like the response to the 2009 influenza pandemic, has been to call for a series of “top down” efforts to dramatically upgrade healthcare systems (especially surveillance), and make large-scale investments in internationally coordinated programs to develop new vaccines and treatments. Little thought seems to have been given to the difficulty of choosing which of the many virus threats should receive priority or, if vaccines and treatments could be developed, how they might be used. For example, the much-heralded success of the Ebola vaccine trial in Guinea (283) depended on an existing human infrastructure that made ring vaccination possible: accurate contact tracing and tracing the contacts of all contacts. This human infrastructure will not exist in most countries when a new epidemic or pandemic virus first appears. Moreover, it will be impossible to vaccinate entire populations beforehand when the identity of the virus that might eventually emerge is not known. In all likelihood, these vaccines will first be given to laboratory and healthcare workers, and only later to populations at risk.
The development of new drugs that target emerging viruses also faces significant limitations. If they are to be specific for each virus, the identity of the next epidemic or pandemic virus will not be known, so choosing which drug to develop will be a matter of guesswork. If newly developed antiviral drugs have broad-spectrum activity, they will still be expensive, in limited supply, and unfamiliar to most physicians. Furthermore, they might be no more effective than the agents that were tested against Ebola (150-154).

A conference held in November 2015 considered (once again) the lessons that should be learned from the Ebola crisis and how they might guide the response to future outbreaks (284). In considering the need for coordinated research, experts agreed that an effective response required more than the input from biomedical scientists; it also required the contributions of engineers, social scientists and ethicists. Yet, the examples given for needed research were biomedical: (I) studies of the human-animal interface; (II) contributions of molecular virology and immunology to understanding population herd immunity (this was considered a crucial area for research); and (III) better vaccines and treatments (although only vaccines were discussed). Once again, the emphasis was on “top down” international cooperation and synergistic action led by WHO. There was no mention of the need for research on treating the host response.

The idea of treating the host response to an emerging virus disease is at least a decade old (120-122,285,286), but it has received little or no attention from WHO, other international institutions, and the scientific community (142; DS Fedson, unpublished observations). Nonetheless, phenotypic observations by physicians and clinical epidemiologists have identified several inexpensive generic drugs that modify the host response to critical illness and improve survival.

These generic drugs should be tested, both alone and in combination, in animal models of emerging virus diseases and other models of acute “everyday” critical illness (e.g., sepsis, influenza, pneumonia).

Promising drugs should be further investigated to define the molecular mechanisms that explain their effectiveness.

Companies that produce these generic drugs should be identified to determine their production and surge capacities, logistical systems for global distribution, and costs to public programs.

An international process should be established to monitor and/or coordinate the distribution of these generic drugs in everyday use and in the event of a Public Health Emergency of International Concern.

Public and foundation funding should support laboratory and clinical research and the development of clinical trial protocols and infrastructures for testing generic drugs that could be used to treat patients with:

- acute “everyday” critical illness (e.g., sepsis, seasonal influenza, pneumonia), and
- acute critical illness that occurs immediately after the emergence of a new virus that threatens to cause a severe epidemic or pandemic.
patients with cardiovascular diseases, they are familiar to physicians everywhere. In addition to treating patients with acute critical illness, experience with outpatient treatment in patients with influenza (Table 3) (130), sepsis (79) and pneumonia (Table 1) (3) suggests that these drugs might also be used in prophylaxis; for example, they could be given to healthcare workers and contacts of patients with Ebola virus disease.

The laboratory and clinical research needed to study this approach to treatment does not require “top down” international coordination. Many reports show it could be undertaken by individual scientists or groups of investigators, many of whom could and should come from low- and middle-income countries (287). If their research conclusively demonstrates the effectiveness of these drugs, they could be used to treat patients infected with many emerging viruses. Because these drugs are generic and inexpensive, global supplies are huge. Consequently, they could be used in any country that has a basic healthcare system, and treatment could be given on the very first epidemic or pandemic day.

There is a strong possibility that a “bottom up” approach to treatment using inexpensive generic drugs could reduce mortality in the next Ebola-like epidemic or the next influenza pandemic. In doing so, it could make an immeasurable contribution to global health, global equity and global security.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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