

What treating Ebola means for pandemic influenza

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Abstract Almost all new treatments being developed for the next influenza pandemic target the virus. During the Ebola crisis in West Africa, patients were treated with an inexpensive generic statin/angiotensin receptor blocker combination that appeared to greatly improve survival. These drugs target the host response, not the virus, and probably reverse endothelial dysfunction. Scientists and health officials have shown little interest in this idea. Yet, during the early months of the next pandemic, vaccines will be unavailable and treatment options will be limited. Physicians should be prepared to undertake clinical trials of widely available generic drugs to determine whether they improve survival in patients with seasonal influenza, other emerging virus diseases, and other forms of acute critical illness. Public health officials should give these studies their strong support. If successful, they will suggest a ‘bottom up’ approach to patient care that could be implemented worldwide on the first pandemic day.

Keywords Ebola · Pandemic influenza · Host response · Endothelial dysfunction · Statins · Angiotensin receptor blockers · Emerging virus diseases

Introduction

Physicians and public health officials expect a new influenza pandemic and are concerned it might be extremely severe. Their pandemic preparedness plans focus on developing new vaccines and treatments that target the influenza virus, but pandemic vaccines will not be available for the first 6 months, and antiviral

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treatments might not be very effective. During this period, millions of people could die.

An experience during the recent Ebola outbreak in Sierra Leone (2014–2016) suggests that inexpensive generic drugs might be used to treat patients with pandemic influenza and other emerging virus diseases. These drugs target the host response to infection, not the virus itself. In Sierra Leone, they appeared to bring about substantial improvement in Ebola patient survival. This treatment experience was unconventional, poorly documented, and ethically complicated, and it has been dismissed by international scientists and health officials. Instead, this elite group has called for complex and costly ‘top down’ initiatives (directed by themselves and their chosen colleagues) to develop new treatments that target these viruses. They find it difficult to accept the idea that a ‘bottom up’ approach to treatment that targets the host response—developed by practicing physicians—might be effective.

The arithmetic for a global influenza pandemic is unforgiving. Physicians and public health officials cannot count on vaccination and antiviral treatment to reduce pandemic mortality; they will need something else. This article explores what this might be.

The Ebola crisis and clinical trials of new treatments that target the virus

The Ebola crisis in West Africa (2014–2016) has come and gone. More than 11,000 people are reported to have died, but overall mortality was probably much higher. Public health measures brought the outbreak under control, but in the absence of licensed treatments, options for patient care were limited. Mortality rates among reported cases were usually 50–60% [1], although outcomes were considerably better among Ebola virus-infected healthcare workers who were evacuated and received intensive care in modern facilities [2].

Several new investigational treatments targeting the Ebola virus were tested in clinical trials in West Africa (Guinea, Liberia, Sierra Leone): antiviral agents, convalescent plasma, and monoclonal antibody preparations [3, 4]. None of these agents brought about significant improvement in patient survival. Journalists described these findings as a “thin scientific harvest” [5].

Ebola scientists believe that effective treatments must target the Ebola virus, and that more potent antiviral drugs might be needed to control virus replication [3]. They base their view on the finding that Ebola mortality is directly correlated with blood virus load, although evidence of association is not necessarily evidence of causation [6]. Moreover, a study of influenza virus infection in mice has shown that changing the host response is associated with significant improvement in survival without affecting virus load [7]. This study (and many others) suggests that treating the host response to infection instead of targeting the virus might be an effective way to care for patients with Ebola and other emerging virus diseases.



Treating the host response to Ebola in Sierra Leone

In Sierra Leone, local physicians treated consecutively approximately 100 Ebola patients with a combination of a statin (atorvastatin) and an angiotensin receptor blocker (ARB; irbesartan) [8, 9]. They noted “remarkable improvement” in their patients: only three are known to have died. These findings were not obtained in a formal clinical trial, but they were documented extensively in letters and memoranda shared by these physicians and local health officials [8, 9, DS Fedson, unpublished observations]. Unfortunately, there was no financial or logistical support for a formal clinical trial and local health officials and representatives of the World Health Organization (WHO) and Médecins Sans Frontières (MSF) actively opposed statin/ARB treatment [8, 9]. Fortunately, a Norwegian physician purchased supplies of the drugs himself and arranged to send them to Sierra Leone.

Combination statin/ARB treatment targets, among other things, endothelial dysfunction and increased vascular permeability, which are central pathophysiological disturbances seen in Ebola patients [8, 9]. Cardiologists know that combining these two drugs gives better results than using either agent alone [10]. Both drugs maintain or restore vascular barrier integrity, largely (although not necessarily exclusively) through their effects on the angiotensin/Tie-2 and ACE2/angiotensin-(1-7)/Mas signaling axes [11].

To their surprise, physicians who treated Ebola patients observed that those who were co-infected with malaria had increased survival [12]. Many of these patients had been treated with artesunate–amodiaquine [13]. In addition to its anti-malarial activity, artesunate helps restore endothelial barrier integrity [11, 14]. Moreover, both statins and ARBs have beneficial effects in mouse models of cerebral malaria (discussed in [11]).

What the Ebola experience means for treating pandemic influenza

Many lessons have been learned from the Ebola treatment experience in Sierra Leone [11], but several deserve special emphasis for what they might mean for treating patients with pandemic influenza. These lessons also suggest the same approach might be used for the syndromic treatment of patients with seasonal influenza, other emerging virus diseases, and other forms of acute critical illness.

Treating the host response is more than an adjunct to antiviral treatment

Ebola scientists regard treating the host response as an adjunct to antiviral treatment [3]. A few of the patients treated with the statin/ARB combination were also treated for ≤ 3 days with clomiphene, a selective estrogen receptor blocker that had been shown in experimental studies to target the Ebola virus [8, 9, 11]. This does not mean that statins (or ARBs) do not have antiviral effects. Several laboratory studies have shown that cholesterol pathways are essential for the replication of many



viruses, including Ebola and influenza viruses [15]. Moreover, studies of influenza and Ebola virus infection in cell culture convincingly show that statins have antiviral effects [16, 17].

The assumption that antivirals are essential for patient care and that host response treatment is only an adjunct to antivirals is probably mistaken [11]. Furthermore, if rhesus macaques (non-human primates, NHPs) are considered the ‘gold standard’ model for determining which treatments should be tested in Ebola patients, scientists should demonstrate in rhesus macaques the endothelial dysfunction seen in patients (which they have not done), and then use Ebola virus-infected NHPs to test drugs that restore endothelial barrier integrity [11].

A case series is a legitimate way to discover something new

There was a rigorous debate among Ebola scientists and health officials over which study designs would be acceptable for testing investigational Ebola treatments. Several different methods were eventually used in clinical trials [3, 4]. Unfortunately, physicians and health officials in Sierra Leone who treated Ebola patients with statins and ARBs documented their experience incompletely and unconventionally [8, 9]. The authors of one review of the Ebola treatment trials concluded, “... it is impossible to draw any meaningful conclusion” from the statin/ARB experience [4]. Another antiviral expert said it was “extremely inappropriate” to publish these findings (DS Fedson, unpublished observation). Nonetheless, what happened in Sierra Leone can be regarded as a historically controlled case series, similar in this respect to the JIKI trial of antiviral (favipiravir) treatment in Guinea [18].

In early August 2014, the idea of treating the host response to Ebola was first suggested to Ebola scientists and WHO staff [19, 20, DS Fedson, unpublished observation]. One Ebola scientist thought it was a terrible idea, and WHO staff expressed serious doubts it would work. Later, in January 2015, WHO staff were told of the apparent success of treating Ebola patients in Sierra Leone with the statin/ARB combination (DS Fedson, unpublished observations); again they showed little interest. One month later, one of the healthcare workers who had treated some of these patients attended an Ebola meeting at WHO headquarters. When he was asked for information about his experience, he replied “the data will not be forthcoming” (DS Fedson, unpublished observation). One of Sierra Leone’s senior health officials later told an international journalist that statins and ARBs had never been given to Ebola patients (DS Fedson, unpublished observation), although there is incontrovertible evidence that contradicts his statement (DS Fedson, unpublished observation). Ebola scientists and WHO staff have never sought to directly validate the statin/ARB treatment experience in Sierra Leone, yet, it is difficult to imagine that local physicians would have treated such a large number of patients (when they were not obligated by a clinical trial protocol to do so) if treatment were having no effect on patient survival.

A formal clinical trial of treating the host response to Ebola may never be undertaken. Although a case series is generally considered to provide weak evidence, it often gives the first indication of something new, surprising, and



important [21]. Moreover, when the benefits of treatment exceed by 5- to 10-fold those of untreated historical controls (as was seen in Sierra Leone), a randomized controlled trial may not be needed [22]. In addition, the US National Academies of Sciences, Engineering and Medicine (NASEM) has concluded that an uncontrolled clinical trial of a previously untested treatment can be considered in any situation in which (1) the disease has a uniformly poor prognosis; (2) no other treatment is available to serve as a control; (3) the proposed treatment is known to be safe; (4) the benefits of treatment would be sufficiently large to make interpretation of the results unambiguous; and (5) its underlying scientific rationale is

Table 1 An agenda for clinical research on treating the host response to pandemic influenza and other emerging virus diseases

Choose drugs that are
Known to modify mechanisms involved in the host response to infection
Safe in patients with critical illness
Produced as inexpensive generics
Widely available in low- and middle-income countries
Familiar to practicing physicians
Likely to affect important outcomes (e.g., 28-day mortality)
Before the emergence of a new virus
Undertake observational studies and prospective clinical trials of treatment in patients hospitalized with every day acute critical illnesses, e.g., seasonal influenza, community-acquired pneumonia, sepsis
Study outcomes in both children and adults
Evaluate outcomes in hospitalized patients who are treated with these drugs, both individually and in combination
Prepare for clinical studies to be undertaken when a new influenza or other virus emerges
Plan observational and prospective studies of treatment to be undertaken immediately upon the emergence of a new virus
Consult with scientists who understand the biology of the host response (e.g., vascular biology, mitochondrial biogenesis, immunometabolism) and the activities of candidate treatments on the host response
Choose two or three drugs for clinical trials, including combination treatment
Prepare clinical trial protocols for children and adults
Consult with statisticians on study designs and plans for evaluating the results
Involve a local ethics review committee
Organize a data safety monitoring board
Obtain logistical and financial support
Assemble networks of physicians who will participate in multi-center trials, if needed
Plan what to do with the results
Identify local sources of supply for potentially efficacious drugs, quantities usually supplied, capacities for surge production and distribution, potential need for stockpiling, and logistics for delivery
Determine drug costs for public programs
Prepare plans to communicate trial results to physicians, public health officials, and the public

Adapted from [55]



so strong that a positive result should be widely accepted [23]. All of these conditions were met by the treatment experience in Sierra Leone [24] (Table 1).

Recently, the former Director of the Centers for Disease Control and Prevention in the United States (CDC) wrote that a case series can make important contributions to public health decision making [25]. At a minimum, the experience in Sierra Leone suggests that the clinical equipoise necessary to justify a randomized controlled trial of treatment that targets the host response to Ebola may no longer exist [11].

The Ebola treatment experience was ethically complicated

The response to the Ebola crisis in West Africa was fraught with ethical problems at many levels [26]. Health officials quarantined some communities and challenged traditional community behaviors (e.g., burial practices). Patients had to be isolated, separating them from their families. Inadequate personal protective equipment compromised the ethical responsibility of healthcare workers to protect their patients. Medical authorities had to reconcile different standards of clinical care for infected healthcare workers and ordinary Ebola patients, including deciding who would have access to investigational treatments. Because there were no licensed treatments for Ebola, there was great interest in clinical trials of these new agents.

During the period from 11 August to 20–21 October 2014, WHO held three meetings to discuss ethical issues related to clinical trials of new Ebola treatments [27]. The participants agreed that clinical trials of promising investigational agents should be undertaken, that the agents should be studied scientifically, and that monitored use of unregistered and experimental interventions (usually known as ‘compassionate use’) by Data Safety Monitoring Boards would be acceptable. They also agreed that community engagement and approval by a local ethics committee were essential. Informed consent was ethically required, although in some circumstances, ‘surrogate’ consent would be acceptable. The WHO advisers agreed to consider “all scientifically recognized methodologies and study designs.” Among those considered acceptable were single arm non-comparative trials, i.e., historically controlled case series. Despite the high risk of bias, these studies would be “most interpretable” if the results were “especially dramatic” [27].

After the Ebola outbreak was brought under control, the WHO Research Ethics Review Committee (WHO-ERC) published a report on the clinical trial protocols it had reviewed [28]. Because statin/ARB treatment in Sierra Leone had not been undertaken according to a WHO-approved protocol, it was not mentioned in the WHO-ERC report.

Two reports on the statin/ARB Ebola treatment experience [8, 9] described the conditions under which the drugs had been sent to Sierra Leone. It was the understanding of the physician who donated the drugs that government ministers, the Office of National Security, the Pharmacy Board of Sierra Leone (PBSL), and local physicians would be responsible for the scientific and ethical guidance that would govern Ebola treatment. The two reports indicate unambiguously that the drugs were to be used according to whatever arrangements local officials deemed appropriate.



A systematic review has reported on whether the Ebola clinical treatment trials in West Africa adhered to ethical guidelines [29]. The authors of the report excluded the experience in Sierra Leone because it appeared that “giving 100 consecutive patients atorvastatin and irbesartan constituted ‘compassionate use’ and did not require ethical approval” [29]. The authors of this review mistakenly assumed that all four authors of one of the two statin/ARB treatment reports (DSF, SMO, JRJ, and OMR; [8]) had known of plans to give the two drugs to Ebola patients, when in fact three of the authors (DSF, SMO, and JRJ) first learned that they had been given in late November 2014, several weeks after news first emerged that treatment appeared to have been successful. In response to this news, the Registrar of the PBSL asked local health officials and physicians several questions about how the drugs should be further studied. Two of these authors (SMO and DSF) learned of his inquiry and immediately wrote to the PBSL with suggestions on how these studies could be structured. They wrote several follow-up letters to the PBSL and also wrote to local physicians and government officials. In addition, DSF sent letters to Ebola scientists, physicians who had cared for Ebola virus-infected healthcare workers who had been evacuated, and to WHO and major institutions involved in the international Ebola response. The letters urged recipients to evaluate the statin/ARB treatment experience in Sierra Leone (e.g., by using a matched pair case–control study) and undertake further studies of this treatment regimen [8, 9]. No replies were received to these letters.

Health officials in Sierra Leone did not permit local physicians who administered statin/ARB treatment to disclose any information on what they had observed. Doing so might have compromised the confidentiality agreements they had signed with (and payments they were receiving from) pharmaceutical companies and international institutions for participating in clinical trials of new investigational treatments. Some of these officials also said they did not want to challenge the position of WHO, which was steadfastly opposed to statin/ARB treatment. Their decisions could be viewed within the context of widespread corruption that was well documented during the Ebola crisis [30].

Pharmaceutical companies undertook clinical trials of several investigational Ebola antiviral treatments and had no interest in studying inexpensive generic drugs that had no commercial potential. Furthermore, if generic treatment were shown to improve survival, this would establish a new standard for Ebola care; in clinical trials of investigational treatments, both control and treated patients would have to be given these drugs. This could dramatically increase the sample size requirements for the trials and probably make it impossible to carry them out.

Academic investigators who participated in the treatment trials were beholden to their sponsors (e.g., pharmaceutical companies, WHO, and foundations such as the Bill and Melinda Gates Foundation, and the Wellcome Trust). They showed no interest in becoming involved in unsponsored studies. Although this is understandable, their silence on the possibility that generic drugs targeting the host response could have been tested did not go unnoticed.

WHO, international foundations, and humanitarian organizations like MSF have missions to relieve suffering and save lives. These organizations would be expected to be indifferent to whether a new Ebola treatment targets the virus or the host



response. They have yet to explain their lack of interest in (or opposition to) testing an approach to treatment based on generic drugs that could have been readily purchased at little cost in local pharmacies [8, 9, 11].

Individuals who speak on behalf of ‘global public health’ argue that efforts to prepare for the next epidemic or pandemic will require a “Coalition of International Stakeholders, which is purpose-built, independent, free of conflicts of interest, possesses expertise in many disciplines, and includes representatives from governments, WHO, academia, the private sector, humanitarian response organizations, and the countries and communities at risk” [31]. The NASEM report concludes that in this way, “the global community has the best chance at being prepared for the next outbreak” [23, 31]. WHO staff believe that “only a global organization such as WHO, which has no vested interests, is equipped to coordinate global medical R&D efforts during epidemics ...” [32].

It is not clear whether these complex ‘top down’ initiatives, which involve only a few hundred elite scientists and health officials, will guarantee that the world will be adequately prepared to confront the next influenza pandemic or epidemic of an emerging virus disease. More important, public health officials should ask whether these ‘top down’ initiatives are the only ethically acceptable way to prepare for what could be a global crisis.

Preparations for the next influenza pandemic focus on vaccine development

Several ‘lessons learned’ reports have analyzed the troubled public health response to the Ebola crisis in West Africa [11, 23, 32]. These reports recommend (1) improving global health governance, in which WHO is expected to play a prominent role, and (2) strengthening national health systems, especially their capacities for disease surveillance and outbreak response. The reports also recommend accelerating research and development of new vaccines, diagnostics, and treatments. Again, WHO is expected to play a prominent role in this work, largely through the creation of public/private partnerships. The cost of these R&D initiatives has been estimated to be \$1 billion per year [11, 33].

The ‘lessons learned’ reports devote considerable attention to vaccine development. For Ebola, health officials regard the success of the rVSV-ZEBOV vaccine trial in Guinea as especially promising [34]. For influenza, WHO considers vaccination as the primary means of responding to the next pandemic [35], and a similar approach can be found in the recently updated pandemic plan for the United States [36]. For other emerging virus diseases, a group of internationally minded individuals and organizations has established the Coalition for Epidemic Preparedness Innovations (CEPI) [37]. CEPI has budgeted \$1 billion over the next 5 years to develop vaccines against two or three emerging viruses, which CEPI intends to enter into efficacy trials during the initial stages of future outbreaks.

No one questions the importance of vaccines in preventing infectious diseases, but ‘top down’ initiatives to accelerate the development of new vaccines for emerging virus diseases will inevitably be slow and costly. Moreover, large-scale production of these vaccines and the development of a human infrastructure for



their distribution and administration to individuals will be even more difficult and complex.

WHO's response to the 2009 H1N1 pandemic had many shortcomings [38] and the Global Action Plan for Influenza Vaccines (GAP) represents one of WHO's efforts to better prepare for the next pandemic [39]. Although the global capacity to produce seasonal influenza vaccines has greatly increased [40], when a new pandemic virus emerges, huge supplies of vaccines must be very rapidly produced. Unfortunately, WHO estimates that it will take 6 months after the emergence of a pandemic virus before the first doses of vaccine can be distributed [41]; in other words, after most of those who will die during the pandemic have already died.

The foundation for successful pandemic vaccination is thought to depend on effective programs for seasonal influenza vaccination. Yet, ongoing analysis of the international production and distribution of seasonal influenza vaccines shows that vaccine uptake has plateaued in several regions and declined in many countries [40]. These discouraging findings emphasize that the human infrastructure necessary for successful vaccination during the next pandemic will not be in place in much of the world. There is no WHO plan for addressing this indisputable need.

Similar problems will face vaccination against other emerging virus diseases. There is no way of knowing whether the candidate vaccines CEPI will develop will match the next emerging virus. Moreover, if the next outbreak of Ebola or an Ebola-like disease is extensive, it is doubtful whether the human infrastructure for 'ring vaccination,' which was essential for the success of the rVSV-ZEBOV vaccine trial [32], will be in place or that it could be rapidly developed. (Ring vaccination involves vaccinating the contacts and contacts of contacts of individuals with the disease). If a population-wide vaccination strategy must be used, it will be even more difficult to vaccinate everyone with one of the CEPI vaccines.

A 'top down' approach to discovering new experimental treatments will be costly and might not be needed

All of the new treatments (e.g., antivirals, monoclonal antibodies) advocated by the 'lesson learned' reports target the viruses themselves. The reports assume that their development will require extensive coordination among international agencies and pharmaceutical and biotech companies (hence public/private partnerships), which will be guided by international experts [11, 23, 32, 33, 41]. To cut down on development costs, some investigators have advocated repurposing existing drugs, but all of the drugs suggested thus far target viruses [42].

Developing pandemic treatments based on inexpensive generic drugs would be more straightforward and much less costly. None of the 'lessons learned' reports acknowledged the potential for repurposing existing drugs to treat the host response [11, 23, 33], and none mentioned the Ebola treatment experience in Sierra Leone. Thus, the reports overlooked its trivial cost: it was funded by a \$25,000 private donation [8, 9]. Moreover, current plans to prepare for the next influenza pandemic fail to mention using generic drugs to treat the host response [35, 36]. Instead, these



‘top down’ plans will require international collaboration, extensive negotiations, and huge costs.

Treating the host response with generic drugs represents a ‘bottom up’ approach to pandemic influenza and other causes of acute critical illness

The Ebola treatment experience in Sierra Leone suggests that generic drugs targeting the host response might be used to treat patients who develop severe illness due to pandemic influenza, other emerging virus diseases, and everyday diseases like seasonal influenza, bacterial sepsis, and community-acquired pneumonia [11]. Clinicians might even use these drugs to treat patients with sporadic diseases such as Hantavirus pulmonary syndrome [43].

All of these diseases are characterized to some extent by endothelial dysfunction. Drugs such as statins, ARBs, and other agents (e.g., PPAR and AMPK agonists) counteract endothelial dysfunction, but they also affect many other aspects of the host response: e.g., pro- and anti-inflammatory cytokines, nitric oxide and redox metabolism, coagulation pathways, complement activity, macrophage and T cell polarization, and mitochondrial biogenesis (see Table 1 in [44]) [11]. They undoubtedly have major effects on immunometabolism [45, 46]. That said, several clinical trials and observational studies have failed to demonstrate convincingly that statin treatment by itself improves outcomes in patients with sepsis and acute respiratory distress syndrome (there are few such studies of ARBs and other immunomodulatory drugs). The limitations of these studies have been discussed previously [11, 44].

Whatever the mechanism(s) by which these generic drugs act, they have the potential to improve outcomes in patients with many forms of acute critical illness. Clinicians could administer them individually or in combination, with or without concomitant antiviral treatment. Equally important, these drugs are produced in many developing countries and are widely available in every country with a basic healthcare system. Because they are familiar to practicing physicians, they could become a common feature of a ‘bottom up’ approach to the syndromic management of patients with critical illness. The cost of treating an individual patient would be far less than the cost of any of the investigational agents that were tested in Ebola patients [3, 4, 11]. Moreover, the drugs would be available for patient care on the first pandemic or epidemic day. The global public health impact of this approach to treatment could be immense.

Scientists and health officials have been reluctant to accept the idea of treating the host response

Given the potential advantages of treating the host response, it is unclear why an idea that is more than 10 years old [47] continues to be ignored. This delay is a reminder that the struggle to introduce a new scientific idea into clinical practice can be time-consuming and often very difficult.

Behavioral economists have shown convincingly that biases, social influences, and herding instincts among scientists and health officials can be hugely important factors



that delay acceptance of a new idea [48, 49]. When decisions have to be made, losses are valued more than gains, and the endowment effect, loss aversion, and status quo bias have become central tenets of modern economic thinking [50]. For scientific innovation, these factors can “distort the evolution of knowledge if scientists are reluctant to accept an alternative explanation for their observations” [49]. Thus, virologists who have worked for decades to develop treatments targeting the Ebola and influenza viruses find it difficult to shift their focus to a new and unfamiliar target. For them and their sponsoring institutions, the reputational and financial costs of accepting this new scientific idea are large and threatening [11].

When public health officials (including those at WHO) seek scientific guidance on policy, they often call on a narrow range of expert advisors [51]. For pandemic influenza, Ebola, and other emerging virus diseases, decision makers almost always turn to virologists, epidemiologists, and public health officials. They do not seek guidance from practicing physicians with expertise in critical care or investigators who understand the biology of the host response and the cell signaling effects of generic drugs. Yet it is experts like these who are best able to provide critical guidance on how to treat patients with pandemic influenza.

Public health officials must not forget the 1918 influenza pandemic

Among all emerging virus diseases, the threat of the next influenza pandemic elicits greatest concern. Earlier worries about influenza A(H5N1) viruses have been superseded by concern about influenza A(H7N9) viruses. Recently, investigators in China have shown that although 74% of 1241 patients hospitalized with H7N9 influenza received antiviral treatment, 40% of them died [52]. Thus, concern about the threat of an H7N9 pandemic is understandable.

In 1918, an estimated 50–100 million people died of pandemic influenza worldwide, more than the number who died in World War I. When the next pandemic virus emerges it will spread rapidly, but pandemic vaccines will not be available for at least 6 months [35]. Resources for patient care will be severely limited in all countries.

Several years ago, a physician recalled his harrowing experiences as a medical student in 1918 when he cared for pandemic patients [53]. Given the inadequacies of current preparedness plans, physicians who will care for patients during the next pandemic might experience something similar to what he went through a century ago. Public health officials must anticipate the extraordinary difficulty physicians and their patients may face with the next pandemic. They must also accept responsibility for ensuring that what happened in 1918 does not happen again.

Physicians and public health officials must take the initiative in undertaking clinical trials of host response treatment

I have seen no meaningful interest on the part of scientists and health officials responsible for national and international pandemic preparedness in the possibility that a simple approach to patient care based on inexpensive and widely



available generic drugs might save countless lives [11, 44, 47, 54]. For this reason, physicians must be prepared to undertake clinical trials *on their own* to demonstrate convincingly whether this approach to treatment might actually work [55]. Public health officials must be prepared to give them strong support. These clinical trials should not be limited to developed countries; it is essential that physicians and public health officials in low- and middle-income countries also become involved [55, 56].

This work should begin as soon as possible because organizing clinical trials after the emergence of a new pandemic virus could take so much time that the pandemic might be over before the trials get off the ground [57, 58]. The 2009 influenza pandemic showed that “research from a ‘standing start’ is not possible; it must be planned in advance, pre-approved and the infrastructure to execute must exist.” [58]. An agenda for clinical research on treating the host response has recently been published (Table 1) [55]. Physicians and their colleagues in public health should consult the website for the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [59]. ISARIC has developed flexible protocols that could be used for studying these generic treatments.

Conclusion

More than a decade ago, an article in this journal suggested that treating the host response might be an effective way for ‘have not’ (i.e., low-resource) countries to confront the next influenza pandemic [60]. Since then, the laboratory and clinical evidence to support this idea has grown stronger [11, 44, 54–56]. When the next pandemic virus emerges, the world might be confronted with a social, political, and economic crisis of unimaginable dimensions.

Public health officials need to recognize that several inexpensive generic drugs that physicians use for patient care every day might be used to reduce pandemic mortality. For this reason, they must vigorously advocate for and generously support the clinical trials needed to show convincingly whether these drugs will be effective. Clinical investigators should undertake these trials in patients with many forms of acute critical illness before the emergence of the next pandemic virus [55]. There is no guarantee that any of these trials will be successful, but if they are, the findings could be immensely important for global health, global equity, and global security. This is a lesson that physicians and public health officials in all countries must be prepared to learn.

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