Indian J Med Res 150, September 2019, pp 217-220
DOI: 10.4103/ijmr.IJMR_2034_18

Quick Response Code:

Perspective

Influenza pandemic preparedness: A special challenge for India

This past year, we commemorated the 100th anniversary of the 1918 influenza pandemic, which is estimated to have killed 50-100 million people worldwide[1]. Its impact in India was especially severe; 10-20 million people may have died[2,3]. Since 1997, influenza scientists and public health officials have been concerned about a potential pandemic caused by the highly virulent avian influenza A(H5N1) virus[4]. More recently, concern has been shifted to the H7N9 virus. In one study of 1241 hospitalized H7N9 patients in China, 70 per cent were treated with antiviral agents, but the overall case fatality rate was still 40 per cent[5]. A recent study has estimated that during the next pandemic, almost 33 million people will die during the first six months[6]. Thus, regardless of which new influenza virus emerges, the risk of a devastating global pandemic is alarmingly real.

Currently, public health officials are counting on vaccines as the first line of pandemic defence. The World Health Organization (WHO) has led a vigorous effort to expand seasonal influenza vaccine production in low- and middle-income countries, including India[7,8]. Seasonal influenza is responsible for appreciable morbidity and mortality in developing countries[9], and expanded vaccine production might reduce this burden by improving vaccination rates. International trends, however, are not encouraging. An ongoing survey of 201 countries has shown that annual influenza vaccine distribution rates in many countries have plateaued, and in some, the rates are actually falling[10]. In the countries of Southeast Asia, the eastern Mediterranean and Africa, which account for at least half the global population, hardly any seasonal influenza vaccine is used. Moreover, it will take time to produce pandemic vaccines, so they will not be available in any country during the first six pandemic months[11].

Physicians count on antiviral drugs to treat individual patients[12]. Anti-neuraminidase inhibitors are only modestly effective in reducing mortality due to seasonal influenza, and antiviral resistance is always a threat. Newer antiviral drugs are being developed, but even if they are efficacious, they may be no more effective than the current antivirals. In addition, the development of antiviral resistance is also a possibility. Thus, given the absence of both pandemic vaccines and highly effective antiviral treatments, it takes little imagination to recognize that human experience during the next pandemic could be similar to what it was 100 years ago[13].

Not everyone infected with influenza virus dies. In the 1918 pandemic, approximately one-third of the human population was infected but a much smaller proportion died. Moreover, pandemic mortality was much higher in young adults than in children. Thus, for each individual, the host response seems to be a central determinant of disease severity[14]. This gives us reason to be hopeful; instead of targeting the virus with vaccines and antivirals, physicians might be able to improve survival by treating patients with drugs that modify the host response to infection.

The idea of treating the host response is >10 yr old[15], and it is supported by a large body of experimental evidence and several observational studies[16-18]. The host response may involve mechanisms that enhance resistance (which reduces pathogen burden) or tolerance (which reduces the impact of infection). In 1918, mortality rates were much lower in children than those in young adults, but the better survival of children was not unique: similar age-related mortality differences have been seen with other virus and bacterial diseases[16]. Recently, this difference has been experimentally reproduced in pre- and post-pubertal mice that were either infected with an influenza virus or treated with endotoxin[19]. Because influenza virus titres and endotoxin levels were similar in both groups, the better survival of pre-pubertal mice suggested that

they were more tolerant, not more resistant. Their better tolerance likely reflects the heritage of evolution.

Among the drugs that have received attention for host response treatment are statins and angiotensin receptor blockers (ARBs). During the Ebola outbreak in Sierra Leone in 2014, combination treatment with these two drugs apparently led to "remarkable improvement" in the patient survival[18]. These drugs have multiple beneficial effects on the host response, including the restoration of endothelial barrier integrity, a central abnormality in the pathogenesis of acute lung injury[18,20]. They also accelerate the return of mitochondrial biogenesis, affect T-cell and macrophage polarization and modify the 'cytokine storm'[16,18]. Their potential effectiveness in treating human influenza has been suggested by the activity of an experimental drug that specifically restored endothelial barrier integrity in a mouse model of influenza[21]. In this study, drug treatment significantly improved survival without affecting virus replication, whereas antiviral treatment alone was ineffective. Other investigators have shown that not only do statins and ARBs restore endothelial barrier integrity, they reduce virus replication[22,23]. Other generic drug combinations might also be used to treat the host response to influenza[24] and sepsis[25].

The idea of treating the host response to pandemic influenza has a highly plausible scientific rationale, but for global public health it is overwhelmingly compelling: simply put, there is no available practical alternative that physicians might use to reduce pandemic mortality. Many of the drugs being considered are produced as inexpensive generics in developing countries, including India. These drugs are widely available and are used by physicians in the daily care of patients. In spite of this, influential influenza scientists and health officials (including those at WHO) have shown no interest in this idea. Several reasons have been invoked to explain their lack of interest, including herding behaviour and social bias[26]. The idea of treating the host response means they risk losing power, influence, reputation and financial support[18].

In the absence of interest on the part of the usual authorities, people everywhere need to ask 'who is responsible for global pandemic preparedness?' Should we depend on a 'top down' process in which a small group of elite scientists and health officials decide which interventions to study in the hope that one or more of them might affect the course of the next global pandemic? Should these elites be allowed to exclude from consideration an alternative 'bottom up' approach to patient care that is scientifically plausible, eminently practical and could have an immense impact on global health, equity and security? The answer to this question is obvious. If treatment with inexpensive and widely available generic drugs could be convincingly shown to work, patients in any country with a basic healthcare system could be treated on the first pandemic day. It follows that in the absence of support for this idea, clinicians might have to undertake studies on their own to show that treating the host response is effective[27]. This includes physicians in India. An agenda for this research has been published (Table)[27].

It is important to recognize that treating the host response is an approach that might be used in patients with other forms of acute critical illness. It appeared to work in patients with Ebola[18] and it would probably work in any illness that involves endothelial dysfunction and the loss of vascular barrier integrity, for example, other emerging virus diseases, sepsis, community-acquired pneumonia and even sporadic illnesses like Hantavirus infection[18]. It could also be considered for treating patients with Nipah virus infection, a recent problem in India[28]. This disease is characterized by endothelial dysfunction[29], and statins and ARBs have beneficial effects on endothelial cells, including those in the brain[30,31].

There is no guarantee that treating the host response will be effective, but we urgently need to find out. If a highly virulent and easily transmissible pandemic influenza virus emerges, it will spread rapidly throughout the world, overwhelming healthcare systems everywhere. In the absence of pandemic vaccines and effective antiviral treatments, the only way Indian physicians might reduce pandemic mortality will be to treat seriously ill patients with easily administered inexpensive generic drugs that are already available and that modify the host response to infection. In countries like India, the challenge of the next pandemic must make this the central element of preparedness planning.

***Conflicts of Interest*:** None.

David S. Fedson
57 chemin du Lavoir, 01630 Sergy haut, France
davidsfedson@gmail.com

Received November 5, 2018

Table. An agenda for Indian physicians who will undertake 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 days' all-cause mortality)
Before the emergence of a new virus
Undertake observational studies and prospective clinical trials of treatment in patients hospitalized with everyday illnesses, for example, seasonal influenza, community-acquired pneumonia and sepsis
Study outcomes in children and adults
Evaluate outcomes in hospitalized patients who are treated with these drugs, both individually and in combination
Plan observational and prospective studies to be undertaken when a new virus emerges
Prepare for clinical studies to be undertaken when a new influenza or other virus emerges
Plan observational studies of treatment effectiveness
Consult with scientists who understand the biology of the host response (*e.g.*, vascular biology, mitochondrial biogenesis and immunometabolism)
Choose two or three drugs for clinical trials, especially in combinations
Prepare clinical trial protocols for children and adults
Consult with statisticians on a study design and a plan for evaluating results
Involve a local ethics review committee
Organize a data safety monitoring board
Obtain logistical and financial support
If needed, assemble networks of physicians who will participate in multicentre trials
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, need for stockpiling and logistics for delivery
Determine drug costs for public programmes
Prepare plans to communicate trial results to physicians, public health officials and the public

Source: Ref 27, reproduced with permission

References

1. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: A quantitative analysis. *Lancet* 2006; *368* : 2211-8.
2. Mills ID. The 1918-1919 influenza pandemic – The Indian experience. *Indian Econ Soc Hist Rev* 1986; *23* : 1-40.
3. Chandra S, Kassens-Noor E. The evolution of pandemic influenza: Evidence from India, 1918-19. *BMC Infect Dis* 2014; *14* : 510.
4. Fedson DS, Dunnill P. Commentary: From scarcity to abundance: Pandemic vaccines and other agents for "have not" countries. *J Public Health Policy* 2007; *28* : 322-40.
5. Wang X, Jiang H, Wu P, Uyeki TM, Feng L, Lai S, *et al.* Epidemiology of avian influenza A H7N9 virus in human beings across five epidemics in mainland China, 2013-17: An epidemiological study of laboratory-confirmed case series. *Lancet Infect Dis* 2017; *17* : 822-32.
6. Gates B. Innovation for pandemics. *N Engl J Med* 2018; *378* : 2057-60.
7. Gellin BG, Qadri F. Preparing for the unpredictable: The continuing need for pandemic influenza preparedness. *Vaccine* 2016; *34* : 5391-2.
8. World Health Organization. *Global influenza strategy 2019-2030*. License: CC BY-NY-SA 3.0 IGO. Geneva: WHO; 2019.
9. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, *et al.* Estimates of global seasonal influenza-associated respiratory mortality: A modelling study. *Lancet* 2018; *391* : 1285-300.

10. Palache A, Abelin A, Hollingsworth R, Cracknell W, Jacobs C, Tsai T, *et al.* Survey of distribution of seasonal influenza vaccine doses in 201 countries (2004-2015): The 2003 World Health Assembly resolution on seasonal influenza vaccination coverage and the 2009 influenza pandemic have had very little impact on improving influenza control and pandemic preparedness. *Vaccine* 2017; *35* : 4681-6.

11. World Health Organization. *Influenza vaccine response during the start of a pandemic. Report of a WHO informal consultation*. Geneva, Switzerland: WHO; 2015.

12. Davidson S. Treating influenza infection, from now and into the future. *Front Immunol* 2018; *9* : 1946.

13. Starr I. Influenza in 1918: Recollections of the epidemic in Philadelphia 1976. *Ann Intern Med* 2006; *145* : 138-40.

14. Pirofski LA, Casadevall A. The damage-response framework as a tool for the physician-scientist to understand the pathogenesis of infectious diseases. *J Infect Dis* 2018; *218* : S7-11.

15. Fedson DS. Pandemic influenza: A potential role for statins in treatment and prophylaxis. *Clin Infect Dis* 2006; *43* : 199-205.

16. Fedson DS. Treating influenza with statins and other immunomodulatory agents. *Antiviral Res* 2013; *99* : 417-35.

17. Fedson DS. How will physicians respond to the next influenza pandemic? *Clin Infect Dis* 2014; *58* : 233-7.

18. Fedson DS. Treating the host response to emerging virus diseases: Lessons learned from sepsis, pneumonia, influenza and Ebola. *Ann Transl Med* 2016; *4* : 421.

19. Fedson DS. Influenza, evolution, and the next pandemic. *Evol Med Public Health* 2018; *2018* : 260-9.

20. Hough RF, Islam MN, Gusarova GA, Jin G, Das S, Bhattacharya J. Endothelial mitochondria determine rapid barrier failure in chemical lung injury. *JCI Insight* 2019; *4* . pii: 124329.

21. Sugiyama MG, Armstrong SM, Wang C, Hwang D, Leong-Poi H, Advani A, *et al.* The Tie2-agonist Vasculotide rescues mice from influenza virus infection. *Sci Rep* 2015; *5* : 11030.

22. Mehrbod P, Hair-Bejo M, Tengku Ibrahim TA, Omar AR, El Zowalaty M, Ajdari Z, *et al.* Simvastatin modulates cellular components in influenza A virus-infected cells. *Int J Mol Med* 2014; *34* : 61-73.

23. Yan Y, Liu Q, Li N, Du J, Li X, Li C, *et al.* Angiotensin II receptor blocker as a novel therapy in acute lung injury induced by avian influenza A H5N1 virus infection in mouse. *Sci China Life Sci* 2015; *58* : 208-11.

24. Hung IFN, To KKW, Chan JFW, Cheng VCC, Liu KSH, Tam A, *et al.* Efficacy of clari thromycin-naproxen-oseltamivir combination in the treatment of patients hospitalized for influenza A(H3N2) infection: An open-label randomized, controlled, phase IIb/III trial. *Chest* 2017; *151* : 1069-80.

25. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; *151* : 1229-38.

26. Baddeley M. Herding, social influences and behavioural bias in scientific research: Simple awareness of the hidden pressures and beliefs that influence our thinking can help to preserve objectivity. *EMBO Rep* 2015; *16* : 902-5.

27. Fedson DS. Clinician-initiated research on treating the host response to pandemic influenza. *Hum Vaccin Immunother* 2018; *14* : 790-5.

28. Donaldson H, Lucey D. Enhancing preparation for large Nipah outbreaks beyond Bangladesh: Preventing a tragedy like Ebola in West Africa. *Int J Infect Dis* 2018; *72* : 69-72.

29. Maisner A, Neufeld J, Weingartl H. Organ- and endotheliotropism of Nipah virus infections *in vivo* and *in vitro*. *Thromb Haemost* 2009; *102* : 1014-23.

30. Yi R, Xiao-Ping G, Hui L. Atorvastatin prevents angiotensin II-induced high permeability of human arterial endothelial cell monolayers via ROCK signaling pathway. *Biochem Biophys Res Commun* 2015; *459* : 94-9.

31. Kono S, Kurata T, Sato K, Omote Y, Hishikawa N, Yamashita T, *et al.* Neurovascular protection by telmisartan via reducing neuroinflammation in stroke-resistant spontaneously hypertensive rat brain after ischemic stroke. *J Stroke Cerebrovasc Dis* 2015; *24* : 537-47.