

## COMMENTARY

# From Scarcity to Abundance: Pandemic Vaccines and Other Agents for “Have Not” Countries

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### ABSTRACT

The recent impasse between the Indonesian Ministry of Health and the World Health Organization (WHO) over sharing H<sub>5</sub>N<sub>1</sub> viruses in return for access to affordable pandemic vaccines highlights slow progress in defining an antigen sparing vaccine formulation, developing licensing requirements that meet the needs of populations and obtaining government funding for vaccine trials. Currently, vaccine-producing countries would have difficulty producing enough doses for their own people and few doses would be left over for non-producing (“have not”) countries. Yet within a few months of the onset of a new pandemic, several billion doses of live-attenuated and recombinant hemagglutinin H<sub>5</sub> vaccines could be produced for “have not” countries, provided a new and disruptive system of “top down” management could be organized. In its absence, a “bottom-up” alternative that uses widely available and inexpensive generic agents like statins must be considered. The “have not” countries must continue to put pressure on WHO and leading countries to ensure that they will have access to the interventions they will need.

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It’s no use saying, “we are doing our best.” You have got to succeed in doing what is necessary. (Winston Churchill)

### THE WHO/INDONESIA IMPASSE AND ENSURING ACCESS TO PANDEMIC VACCINES FOR “HAVE NOT” COUNTRIES

In February 2007, the Indonesian Minister of Health announced that Indonesia would stop sending virus specimens obtained from H<sub>5</sub>N<sub>1</sub> influenza-infected patients to the World Health Organization’s (WHO) surveillance laboratories (1). This article discusses vaccines and other agents but does not consider issues related to the use of

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antiviral agents in confronting the next pandemic. Many patients with H<sub>5</sub>N<sub>1</sub> infection have shown limited benefit from treatment with neuraminidase inhibitors and current clinical research is focused on testing larger doses and new antiviral compounds. Moreover, the global manufacturing capacity for these agents is limited and production has been scaled back because of limited demand. See Reuters. Roche says Tamiflu capacity outstrips demand. 26 April 2007 (<http://www.reuters.com/articlePrint?articleId=USL2643587520070426>). If other H<sub>5</sub>N<sub>1</sub>-affected countries had followed Indonesia's lead, WHO's half-century old global system for influenza virus surveillance could have quickly collapsed. Prior to this announcement, Indonesia had freely sent its H<sub>5</sub>N<sub>1</sub> virus isolates to the laboratories of WHO's Collaborating Centers. In addition to studying these viruses, the WHO laboratories routinely sent selected viruses to companies to use in developing vaccines for the next influenza pandemic. WHO has always sent influenza viruses to companies without charge, yet Indonesian health officials realized they would have to pay companies for these vaccines and they regarded this exchange as unfair (1). They now insisted on a revision of this WHO system and a guarantee that Indonesia would have access to an affordable supply of pandemic vaccine.

In an effort to preserve its virus-sharing system, WHO officials met with health officials from several Asia-Pacific countries in Jakarta in late March 2007 (2,3) and with vaccine company representatives in Geneva in late April 2007 (4). The discussions were a prelude to intense negotiations that were conducted at the meeting of the World Health Assembly (WHA) one month later (5). WHO had already taken steps to improve access to pandemic vaccines by facilitating an \$18 million transfer of vaccine production technology to six developing countries (2). WHO had also proposed setting up expert groups to suggest ways to create, maintain, fund and use an international stockpile of H<sub>5</sub>N<sub>1</sub> vaccines. Missing from the WHO announcements, however, was any mention of whether accelerated technology transfer, vaccine stockpiles or "legally binding agreements" between companies and countries for supplies of pandemic vaccine would address realistically the immediate concerns of Indonesia and other "have not" countries – namely, how can they obtain supplies of pandemic vaccines if they don't produce them.

## SLOW PROGRESS IN DEVELOPING PANDEMIC VACCINES

WHO and the major vaccine companies have come to realize that despite several years of effort, conventional inactivated H<sub>5</sub>N<sub>1</sub> vaccines will be difficult to develop and even more difficult to produce (6–8). Egg-based H<sub>5</sub>N<sub>1</sub> vaccine production requires the use of reverse genetics-engineered seed viruses, but average production yields have been only one-third those obtained for ordinary seasonal vaccine viruses. Moreover, each person will probably require two doses of an antigen sparing, adjuvanted vaccine. Unfortunately, if all of the world's major influenza vaccine companies were to produce such a vaccine according to the best formulation currently known (3.75 µg hemagglutinin (HA) with an adjuvant), the number of doses that could be produced in 6 months would be enough to vaccinate with two doses only 700 million people (7,8). The combined population of the nine countries where these companies are located is 750 million people, and their governments have indicated they will want to vaccinate their own people first. Thus, few doses will be available for people in other countries.

The United Nations System Coordinator for Avian and Human Influenza estimates that almost 100 countries intend to purchase pandemic vaccines (9), indicating that global demand could easily reach several billion doses. There is no way current efforts to develop conventional inactivated pandemic vaccines will be able to meet even a fraction of this demand. WHO has concluded, “most developing countries will have no access to a vaccine during the first wave of a pandemic and perhaps throughout its duration” (10). But access to pandemic vaccines will be a problem not just for developing countries like Indonesia; it will also be a problem for every “have not” country (e.g. Spain and Sweden) that does not produce its own influenza vaccine. It will even be a problem for vaccine-producing countries like the United States that will find it difficult to cover their own populations.

## MISTAKES IN MANAGING PANDEMIC VACCINE DEVELOPMENT

The re-emergence of human H<sub>5</sub>N<sub>1</sub> virus infections in Southeast Asia in 2003 greatly accelerated efforts to develop inactivated H<sub>5</sub>N<sub>1</sub> vaccines. WHO has focused attention on what is needed by convening

meetings to review research findings (11,12), issuing a global action plan to increase vaccine supply (13) and providing guidance on H5N1 viruses that should be used for vaccine development (14). In recent months, several “mock-up” adjuvanted H5N1 vaccines have been licensed in Europe and one non-adjuvanted vaccine has been licensed in the United States. Yet, as noted above, these efforts fall far short of what will be needed to meet world demand.

Until now, pandemic vaccine development has been viewed primarily as a vaccine problem that should be addressed with better science (15), but fundamentally it is a global public health problem that requires better management (7). In the absence of good management, mistakes in at least three key areas have delayed H5N1 vaccine development: failure to require antigen sparing vaccines, failure to focus on protecting populations, and failure to see vaccine development as a government responsibility.

### *Pandemic Vaccines Must Be Antigen Sparing*

In Europe, influenza experts recognized early on that pandemic vaccination would require far greater numbers of doses of inactivated vaccine than are ordinarily used for seasonal vaccination (6,7). This could be achieved only with a vaccine that contains a much lower amount of vaccine antigen than is used for seasonal vaccines. A low dose formulation would require adding an adjuvant, a substance that increases the vaccine’s ability to induce a satisfactory immune response.

In the 1950s, American investigators reported that by adding an adjuvant to influenza vaccine, “a phenomenal economy can be effected in the requirement of antigen” (16). Despite this knowledge, regulatory officials in the United States insisted until recently that an adjuvanted pandemic vaccine would be approved only if there were clinical efficacy data for a similarly adjuvanted seasonal vaccine, something no vaccine company was interested in developing for the US market. They also insisted that the adjuvanted vaccine had to be more immunogenic than its non-adjuvanted counterpart (6,7). Because of these restrictions, the initial H5N1 vaccine trial in the United States was conducted with a non-adjuvanted formulation, with unimpressive results (17). This vaccine formulation recently received a US license, but there is no intention of ever using it. Within

the past year regulatory requirements have been relaxed and efficacy trials of adjuvanted influenza vaccines are no longer required (18). Nonetheless, by not testing an adjuvanted H<sub>5</sub>N<sub>1</sub> vaccine initially, 1–2 years of development time were lost.

*Pandemic Vaccines Must Be Acceptably Immunogenic for Populations*

In licensing a pandemic vaccine, one of the important decisions regulatory officials will have to make will be to choose a vaccine formulation that promises the greatest amount of protection for a population. The principles underlying this decision are illustrated by an example drawn from the published results of the US clinical trial of a non-adjuvanted H<sub>5</sub>N<sub>1</sub> vaccine (Table 1) (17). In this study, 54% of the subjects who received two doses of the highest vaccine dose (90 µg HA) had neutralizing antibody titers  $\geq 1:40$ . (For seasonal influenza vaccines, an antibody titer  $\geq 1:40$  is generally accepted as protective.) The proportions with protective antibody levels were lower with lower strength vaccines. However, if it is assumed that by lowering the amount of HA antigen in each vaccine dose the total number of doses that could be produced would correspondingly increase, choosing a vaccine formulation containing only 15 µg HA per dose would protect the largest number of people (see Table 1).

The example in Table 1 is hypothetical, greatly simplified and does not consider strategies such as giving only one dose of vaccine to each individual. (Prior to the emergence of a pandemic virus, it

Table 1: Formulating a pandemic vaccine that is adequately immunogenic for a population

<i>µg HA per dose</i>	<i>% with neut titer <math>\geq 1:40</math></i>	<i>Number vaccinated</i>	<i>Number protected</i>
90	54	100	54
45	43	200	86
15	22	600	132
7.5	9	1,200	108

Adapted from reference (17).

See text for details.

would be difficult to determine what dose of pre-pandemic HA antigen would effectively prime the immune system to withstand later challenge by natural infection with a true pandemic virus, although experimental studies might provide important clues about what would work (19).) Nonetheless, a decision on how to formulate a pandemic vaccine that will be acceptably immunogenic for a population, not optimally immunogenic for an individual, must consider the principle illustrated in the table. Current regulatory guidelines for licensing pandemic vaccines in the United States fail to mention the importance of this principle (18).

### *Pandemic Vaccine Development Must Be Paid for by Governments*

In the United States, several billion dollars have been spent on H<sub>5</sub>N<sub>1</sub> vaccine development (7). Clinical trials of candidate H<sub>5</sub>N<sub>1</sub> and other potential pandemic vaccines have been sponsored by the NIH and more recently (and more extensively) by the Department of Health and Human Services. The federal government has also committed one billion dollars to accelerate the construction of cell culture-based vaccine production facilities. These facilities are intended to create a “surge” capacity capable of producing 600 million doses of pandemic vaccine in 6 months, but they will not begin producing their first doses for at least 5 years. Understandably, federal efforts for near-term pandemic preparedness have focused intensively on non-pharmaceutical interventions (20).

Federal officials in the United States understand that responsibility for paying for pandemic vaccine development rightfully rests with government, not private industry (6). This understanding is shared by government officials in Japan and China and, to a lesser extent, in Australia and Canada. However, government officials in the five Western European countries where influenza vaccine production facilities are located (France, Germany, Italy, The Netherlands and the UK) have provided virtually no public funding to support H<sub>5</sub>N<sub>1</sub> vaccine trials. (Germany is the sole exception, providing modest support for a trial of one company’s vaccine.) The absence of public funding is all the more alarming because vaccine companies in these five countries supply almost all of the doses of seasonal influenza vaccines used in non-vaccine-producing countries (21).

The lack of government funding in Western Europe has had serious consequences for the types of H5N1 vaccine trials companies have undertaken (7). Because companies have had to pay for the trials, they have been small, not large. Moreover, because European regulatory requirements for “mock-up” pandemic vaccines are stricter than they are for seasonal vaccines, companies have chosen not to test very low dose formulations because they do not want their vaccines to “fail.” Consequently, they have been unable to determine the lowest dose formulation that might meet regulatory requirements and at the same time give them an indication of the largest number of doses they could produce. This understandable caution, if continued, will inevitably limit the number of doses companies will produce.

The crippling effects of European government inaction have been recognized for several years, but neither the governments themselves nor the European Commission has given any indication they will begin providing needed financial support for H5N1 vaccine trials. Instead, governments have been content to purchase modest supplies of higher-dose H5N1 vaccines whose formulations they have had no role in defining. It is inconceivable that the same governments would take a similarly passive role regarding the specifications of the weapons systems they purchase for their national defence forces.

#### THE WHO RESPONSE TO INCREASING SUPPLIES OF PANDEMIC VACCINES FOR “HAVE NOT” COUNTRIES

The WHA resolution that was passed in May 2007 called on the Member States to continue sending their influenza virus samples to the WHO laboratories (5). In order to assist developing countries, it called on WHO’s Director General to (1) develop financing mechanisms for purchasing pandemic vaccines, (2) increase manufacturing capacity to produce these vaccines (technology transfer), (3) establish an international pandemic vaccine stockpile, and (4) ensure fair and equitable distribution of these vaccines at affordable prices. It also called for the establishment of a working group to revise the “terms of reference” for sharing viruses between countries and the WHO laboratories.

It has been evident since February 2007 that a WHA resolution could not satisfactorily resolve Indonesia’s concerns about access to pandemic vaccines, at least in the near term. WHO officials stressed that supplies

of pandemic vaccines would be severely limited for at least the next 5 years (22). In the interim, an international stockpile would address the most urgent needs of developing countries, and early discussions mentioned a stockpile of 40–60 million doses (23). It seems unlikely that a stockpile of this size will be adequate; Indonesia's health minister has said that her country alone would need 22 million doses. In an unrelated but revealing development, WHO has announced it will establish a \$58 million program to provide yellow fever vaccine to 48 million people in 12 West African countries (24). Yellow fever accounts for approximately 30,000 deaths in these countries each year. Thus, for pandemic influenza, WHO appears to be considering a vaccine stockpile of similar size to respond to a global disease threat that might kill a far larger number of people than yellow fever.

Defining the boundaries of the new “terms of reference” for virus sharing may be the most difficult issue to resolve. The WHA resolution states that any use of viruses outside the scope of the terms “would be bilateral activities not requiring the intervention of WHO” (5). A narrow definition of the terms of reference could conceivably absolve WHO of formal responsibility for ensuring access to the enormous number of doses of pandemic vaccine that “have not” countries will seek to obtain. At the time of an imminent pandemic threat, hundreds of simultaneous bilateral negotiations (or attempts at negotiations) between countries and vaccine companies would surely be both chaotic and unsuccessful.

#### NEW APPROACHES TO PANDEMIC VACCINE DEVELOPMENT AND PRODUCTION

If we knew the next pandemic would come 10 years from now, continued progress in vaccine development might solve the global vaccine supply problem. Several pandemic vaccine candidates now in pre-clinical development look promising (15), and one or more will surely move on to clinical trials and eventual licensure. Yet, serious virologists continue to remind us that the pandemic might arrive not in 10 years but much sooner. The specific genetic changes that would be required for an H5N1 virus to develop the capacity for efficient human-to-human transmission and thus lead to pandemic spread are unknown, but the number of changes is probably small (25). For this reason, a way must be found to use existing knowledge and

industrial capacity to produce within a few months enough doses of pandemic vaccine to vaccinate at least 3–4 billion people. This will require new types of vaccines and new methods of production.

Two approaches could be taken that would greatly improve global prospects for developing and producing adequate supplies of pandemic vaccines. One would be to use a live-attenuated vaccine and another would be to use a recombinant hemagglutinin (rHAO) vaccine (8). These vaccines share two important advantages. First, in their seasonal formulations one is already licensed and the other is almost ready to be licensed, something that cannot be said for all other vaccine candidates currently being developed (15). Second and more important, the global industrial capacity to quickly produce billions of doses of both vaccines already exists.

A live-attenuated trivalent vaccine is already licensed for seasonal use in the United States and is available in a refrigerator stable form. An experimental live-attenuated H5 vaccine has induced broad protection against challenge infection in animals (26). Despite early difficulties (27), the prospects for successfully developing a similar H5 vaccine for human use are very good. In the event of a pandemic, it could be produced in the egg-based facilities of current manufacturers, in the cell culture systems that will gradually replace them or even in facilities now used to produce vaccines for poultry (13). Only one dose would likely be required and it could be administered intranasally. Compared with conventional inactivated vaccines, the efficiency of producing a live-attenuated vaccine might increase up to 100-fold (8). If the requisite number of production facilities could be brought on line, several billion doses could be produced in a few months.

A seasonal rHAO vaccine has been shown to be safe and immunogenic, and preliminary studies indicate it provides a level of clinical protection that could lead to licensure in the near future (28,29). A similar vaccine directed against an H5 virus could be produced in pharmaceutical bioreactors that are now used to make high value biopharmaceutical proteins. Assuming that 25% of the global bioreactor capacity could be harnessed for 3 months and that the vaccine could be formulated with an adjuvant in the same way as current inactivated H5N1 vaccines, enough doses could probably be produced within 3 months to vaccinate with two doses more than three billion people (Table 2) (8).

Table 2: Hypothetical number of people who could be vaccinated with 3 months' production of conventional egg-based H<sub>5</sub>N<sub>1</sub> or rHAO H<sub>5</sub> influenza vaccines\*

<i>Amount of HA antigen per dose (µg HA)</i>	<i>Egg-based vaccine<sup>†</sup></i>	<i>rHAO vaccine<sup>‡</sup></i>
10	132 M	1.3 B
3.75	351 M	3.4 B <sup>§</sup>

\* The estimates for both vaccines assume that two doses of adjuvanted vaccine would be required for each person. M indicates million; B indicates billion.

<sup>†</sup> The estimate for egg-based production assumes that yields of reverse genetics-engineered H<sub>5</sub>N<sub>1</sub> vaccine viruses would be 33% of the yields for seasonal vaccine viruses and that the global capacity to produce egg-based seasonal vaccines is 350 million doses (see reference 8).

<sup>‡</sup> The estimate for rHAO production uses yields that are reduced to 25% of those estimated from the company's pilot studies and assumes that 25% (500,000 liters) of the global pharmaceutical bioreactor capacity (2,000,000 liters) could be harnessed for rHAO vaccine production (see reference 8).

<sup>§</sup> In 2005 the world population was estimated to be 6.45 billion people.

Developing either a live-attenuated or rHAO pandemic vaccine would not require any major scientific or technical breakthroughs, although both vaccines would require additional development. Clinical trials would be needed to determine their safety and immunogenicity. Regulatory decisions would have to be made on formulations appropriate for populations. Production sites would have to be selected and bioprocessing and scale-up procedures validated. Intellectual property rights and liability responsibilities would have to be negotiated with governments. Country-specific vaccine demand forecasts would have to be prepared, financing mechanisms for vaccine purchase put in place, and the logistics of production and distribution organized. For the rHAO vaccine, a global stockpile of syringes would be required.

Each of the individual tasks mentioned above would be daunting. Considered together, they would present a challenge unprecedented in scale and complexity. Nonetheless, developing and producing pandemic vaccines for people in all countries must not be viewed as a scientific and technical challenge alone; it is fundamentally one of politics and logistics, and success "in doing what is necessary" will require far more imagination and ambition than has been evident thus far. It will require a steadfast determination to make radical changes and a willingness to abandon the "business as usual" approach that has characterized pandemic vaccine development until now.

MANAGING VACCINE DEVELOPMENT FOR A GLOBAL  
PANDEMIC: LESSONS FROM THE PAST

Several useful lessons for pandemic vaccine development can be found in the experience with vaccine development in the United States during World War II (30). At the time, many people remembered that 80% of US Army casualties during World War I were attributable to the 1918 influenza pandemic. They recognized, in the words of one observer, that “virulent influenza may be more devastating to human health than war itself. ...” (30). In the early 1940s the US Army was aware that uncontrolled infectious diseases could have a serious impact on the war effort, and this led to unprecedented efforts to develop a number of vaccines. In 1941, the Influenza Commission was established and within 2 years an influenza vaccine was developed and its efficacy demonstrated in a clinical trial that involved 12,500 subjects. These results led the Surgeon General to recommend purchasing 10,000,000 doses for military use.

The keys to the success of wartime development of influenza vaccine were (1) an overwhelming sense of urgency brought on by the war itself, (2) the role of the US Army as the “lead user” of the vaccine, (3) a top-down system of governance coordinated by the Army Surgeon General’s Office and the civilian Office of Scientific Research and Development that managed the work of military, academic and industrial scientists and minimized bureaucratic delay and inefficiency, and (4) the appointment of project managers with defined goals and objectives who rapidly integrated and applied scientific knowledge to develop, test, scale up and produce an influenza vaccine. The leaders of this effort recognized that the barriers to developing influenza and other vaccines “were not primarily scientific but organizational in nature ... (and were) ... best overcome by the coordination provided by targeted research and development” (30).

Unlike wartime experience 60 years ago, modern vaccine development has been left largely in the hands of vaccine companies. A notable exception in the United States was the NIH-led program to develop a swine influenza vaccine in 1976; within 5 months, immunogenicity and safety trials were conducted in 6,500 subjects using four different swine influenza vaccines produced by four

different companies. The trials established the vaccine formulation and vaccination schedule required for swine flu vaccination (7).

Although useful insights can be gained from influenza vaccine development during WWII, the challenges for pandemic vaccine development today differ in several important ways. First, the sense of urgency that directly motivated everyone in WWII is not matched by H<sub>5</sub>N<sub>1</sub> influenza, a disease that has affected only a few hundred people in distant countries. Second, it is difficult to define precisely a “lead user” with experience to drive vaccine development when the “lead user” is the entire population of a single country or, indeed, people in all countries. Third, no system of top-down governance has yet been established in any country that integrates the activities of government, academic and industrial scientists and institutions for the purpose of developing, testing, producing and delivering a pandemic vaccine. Nonetheless, although the challenges currently facing pandemic vaccine development are more difficult than those encountered for influenza vaccine during WWII, the lessons of 60 years ago are still instructive.

In the United States, it has been suggested that a master program for pandemic vaccine development be established that matches the scale of the Apollo space program (31). Although the multi-billion dollar scale of the two efforts might be similar, the analogy is not precise; if the Apollo program had been delayed or unsuccessful, there would have been no serious consequences to human wellbeing. In contrast, the consequences of delay or failure in developing and producing pandemic vaccines could be catastrophic. A more instructive (if troubling) analogy would be the Manhattan Project to develop the atomic bomb (32). The purpose of the Manhattan Project was to develop, test, produce and deliver a weapon to win a war. Its most important task was to produce within a very short period of time sufficient quantities of uranium and plutonium to build a bomb (32,33). The Manhattan Project achieved all of its objectives in less than 3 years.

#### WHAT IS MISSING: EFFECTIVE TOP-DOWN MANAGEMENT FOR PANDEMIC VACCINE DEVELOPMENT AND PRODUCTION

Progress in developing H<sub>5</sub>N<sub>1</sub> vaccines has been slow and mistakes have been made because governments have failed to understand

the public health nature of their responsibilities and the absolute necessity for firm, decisive public management of both vaccine development and production. Vaccine companies have not been able to organize these tasks by themselves and they have not tried to do so. They should not be expected to.

Given the international nature of the pandemic threat and the global need for vaccines, the possibility of international management for pandemic vaccine development, production and distribution should at least be considered. The recent WHA resolution on pandemic influenza directs WHO's Director General to move in this direction (5). Whether WHO could manage this by itself is uncertain. WHO has been responsible for many important achievements on behalf of pandemic preparedness, but it is unlikely that it has the authority or the capacity to manage successfully a project of such size and complexity.

To meet international needs, pandemic vaccine development and production will be more likely to succeed if a few governments, the United States foremost among them, accept full responsibility for doing what needs to be done. Their activities must be guaranteed international political legitimacy, cross border operational authority and financial accountability. They would have to include brokering and funding new collaborative arrangements between companies that otherwise would have no reason to work together. Because of its scale and complexity, a common understanding must be reached on whether top-down management by a few countries is desired and achievable. If it is, the work that needs to be done should start immediately. If it is not, practical alternatives must be considered.

It is useful to recall that individual nations and the international community have come up with solutions to manage potentially disastrous economic crises. In the United States, the Strategic Petroleum Reserve was created to manage the economic consequences of an interruption in the supply of oil. On 1 December 2006 the reserve contained 688.5 million barrels with a value (at \$60 per barrel) of \$41.3 billion dollars (34). When the international community was faced with monetary crises in Mexico, Brazil and Southeast Asia in the 1990s, within a few weeks international institutions assembled financial guarantees to manage the crises valued at \$38–120 billion (35). Nothing approaching this level of

investment has been made by any country or the international community to prepare for a global influenza pandemic.

A BOTTOM-UP APPROACH TO CONFRONTING AN IMMINENT  
PANDEMIC THAT COULD BE IMPLEMENTED IN “HAVE NOT”  
COUNTRIES

Unless there are dramatic changes in the current top-down approach to managing the development and production of pandemic vaccines, a successful response to the next pandemic will be beyond the reach of “have not” countries that lack manufacturing capabilities. An effective bottom-up alternative is needed. One possibility would be to use inexpensive generic medications that are produced and available worldwide. Statins, the drugs used to treat high cholesterol levels and prevent heart disease, are among the agents that should be considered (8,36).

The scientific rationale for considering statin treatment and prophylaxis for pandemic influenza is based on their anti-inflammatory and immunomodulatory (pleiotropic) effects (37). Statins work by down-regulating a large number of pro-inflammatory cytokines, and their protective effects have been likened to “reducing the heat under a boiling kettle” (38). They could help control the aberrant innate immune response (cytokine storm) that characterizes human H<sub>5</sub>N<sub>1</sub> infection (39) and could accompany infection with a similarly virulent pandemic virus (40,41).

Recent observational studies have shown that prescriptions for statins are associated with 30%–50% reductions in hospitalizations for chronic obstructive pulmonary disease and pneumonia and 40%–60% reductions in pneumonia and all-cause mortality (8,36). These studies have provided an “epidemiological signal of protection” and clearly indicate the urgent need for additional research. Studies of H<sub>5</sub>N<sub>1</sub> and 1918 influenza in animal models could determine whether statins, with or without concomitant antiviral treatment, are efficacious. In addition, observational studies of inpatient statin treatment of pneumonia patients in and out of influenza seasons could indicate whether statins could benefit patients with seasonal as well as pandemic influenza.

If the benefits of statin treatment and prophylaxis of influenza are confirmed in experimental and clinical studies, this knowledge could

be of immense value for global public health. Generic simvastatin is currently being produced by almost 100 companies, more than half of which are located in China and India. It has recently been added to the WHO list of essential medicines and treatment in a developing country would cost 10 cents a day (42). By comparison, a 5-day course of the antiviral oseltamivir (Tamiflu<sup>®</sup>) in the United States would cost \$60–90 (36). Moreover, unlike vaccines and antivirals, generic simvastatin would be available on the first day of the pandemic.

#### THE CONTINUING AND POSSIBLY IMMINENT THREAT OF THE NEXT PANDEMIC

In countries with cases of H5N1 influenza, 60% of patients still die, in many instances despite the best that medical care can offer. Virologists know that with only a few genetic changes, the H5N1 virus could acquire the capacity for efficient human-to-human transmission (25), and with undiminished virulence it could cause the deaths of hundreds of millions of people, far more than would die as a result of a 1918-like pandemic (43). Health officials in Indonesia and other developing countries understand this and are rightfully concerned. But they also need to understand that if the pandemic is imminent, technology transfer would not occur fast enough and a virtual stockpile of pandemic vaccines could amount to little more than a gesture. With so much at stake, it is not surprising that Indonesia's Minister of Health has said that "a huge gap between rich and poor countries" in access to pandemic vaccines "will perhaps threaten world peace" (44).

Access to supplies of pandemic vaccine for most countries is fundamentally a problem of scarcity. The best solution to a problem of scarcity is abundance. Health officials and political leaders in "have not" countries must impress upon WHO and the governments of leading developed countries the absolute need for disruptive changes in the ways that pandemic vaccines are being developed and will be produced. At the same time, they must urge clinical and laboratory investigators in all countries to look carefully at whether inexpensive and widely available generic medications might offer benefits for pandemic treatment and prophylaxis. Above all else, they must not give in to "pandemic fatigue" because only by

continuing to put pressure on WHO and the leading vaccine-producing countries will they have any realistic hope of successfully confronting the next pandemic.

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