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"Responding to the Threat of Global, Virulent Influenza"

Written testimony before a hearing of
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By

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Chairman Lugar, Senator Biden, and distinguished members of the United States Senate Committee on Foreign Relations. I am honored to appear before you this morning to discuss our nation's response to the threat of pandemic influenza, with special attention to implications for foreign policy and national security.

Since late May of this year, when the Council on Foreign Relations publication *Foreign Affairs* published a special issue on the threat entitled "The Next Pandemic?" we have been pleased to see a marked increase in the level of concern and action regarding the flu threat, both within our government as well as at the highest levels of other governments, international agencies, the United Nations system, trade organizations, and multinational corporations. As we meet here today a major three day flu summit is winding up in Geneva, involving more than 600 representatives of 100 nations. Grim news has poured from that summit, including a World Bank estimate that a pandemic would cost the global economy some $1.35 trillion. The good news is that such a meeting, bringing together rich and poor nations and UN agencies to plan a pandemic response, has happened. The bad news: It was the first such gathering, coming only after the H5N1 virulent avian influenza virus has been in circulation for at least nine years in Asia, has now spread to Europe, and threatens to surface in the next 30-60 days in sub-Saharan Africa.

In recent days we have seen pandemic plans released by the governments of the United Kingdom, Canada, Hong Kong – according to the World Health Organization some 60% of the world's nations have created some type of pandemic plan in recent weeks. Our own government has in the last two months: issued the "Ten Core Principles" of global pandemic response, hammered out in September negotiations between Presidents George W. Bush and Hu Jintao and now signed onto by 88 nations and agencies; released the President's $7.1 billion pandemic budget request; the Department of Homeland Security released its 12-page plan; and the Department of Health and Human Services released a 300-plus page influenza pandemic plan. We are told that a detailed, all-agencies Federal plan will soon be released, offering details that are sorely lacking in those schemes that have, to date, been published.

This is a very good start. But let's be clear – that is all we are seeing, even with pandemic flu threats making the covers of every major news weekly and newspaper in the nation – *a start.*

From the foreign relations perspective of this committee I would like to offer a few key concerns, drawn from the scientific and public health communities.

- **If prognostic forecasts of human death tolls or economic costs are going to be released by "official voices", let's be clear about the motivations behind those numbers, and the data assumptions used in their derivations.** Fear can motivate policy, and conversely low ball estimates may prompt sighs of relief and eventual complacency. Some global and national agencies, concerned that high numbers might lead to public panic or to fret that response agencies are inadequate to the task, have chosen to derive all their numbers from comparatively mild flu data. For example, WHO and CDC have extrapolated their estimates that, at most, the world might experience 7.5 million deaths from virulent flu from the 1968 flu database. That influenza, however, killed roughly 0.6 percent of those humans it infected. That's a far cry from the 55 percent who have succumbed following infection with the H5N1 strain. On the other hand, extrapolating from that 55 percent mortality rate to a global scale would lead to a staggering, terrifying number that cannot possible motivate a reasonable policy response. Reckonings based on a somewhat dampened mortality rate have put the projected death toll as high as 360 million deaths globally, with 1.7 million of them being Americans. It is imperative, when looking either at global mortality data or economic costs, that policymakers demand to know the assumptions used to derive reckonings.

  The two most important assumptions are (1.) the virulence, or mortality rate, of the virus – How many infected people will die? And (2.) the attack rate, or transmissibility of the virus – What percentage of an exposed human population will actually become infected with the given flu strain? There is no way to know the answers to those two points until a virulent, human-to-human transmissible flu emerges. Therefore, Ladies and Gentlemen, it is all guesswork. You should be skeptical of claims, scrutinize the assumptions made to derive any numbers, and avoid basing your policies on them. A quick example: earlier this year the Institute of Medicine estimated that a pandemic flu would cost the United States somewhere between $151 - $166 billion, just for medical care and direct costs to the health system. The larger costs to the U.S. economy due to lost productivity, sustained market failures, projected stock losses and international trade disruptions are considered virtually unknowable. Yet the World Bank this week released its estimates, based on a pandemic that lasts for a full year: $800 billion lost to the Asian economies, plus $550 billion for the U.S. and OECD nations, with no estimates for Africa or most of Latin America, for a ball park total of $1.35 trillion.

  To be honest, I believe the only empirically valid statement that can be made – and that should be used in your policy assumptions – is that a highly virulent, highly transmissible pandemic influenza that circulates the world repeatedly for more than a year will kill more people than all the weapons of mass destruction that have been of concern to this Committee save, perhaps, a thermonuclear exchange. And such a catastrophe will be astoundingly expensive to the global economy, not only in immediate GDP losses, but quite possibly in the form of a long term shock to the entire globalized trade environment.

- **Containment is not possible with currently available health infrastructures and technology, and funding priorities stated to date do not reflect the needs levels.** Two major computer modeling studies published this summer in *Science* and *Nature* demonstrate that only the most Pollyanna of assumptions can possibly result in

containment of an initial outbreak of human-to-human transmissible influenza. WHO's flu leadership has concluded that the agency and its global partners – such as the CDC – would have only 30 days to throw a Tamiflu-and-quarantine ring around an outbreak site before the virus would manage to get into regional, and probably global, circulation. But it's not really even 30 days, as the Achilles heel of all containment strategies are recognition and notification. Local health providers must recognize that an unusually virulent form of flu is in circulation, notify high authorities, send samples to laboratories for confirmation, gain their government's clearance and then officially inform WHO. Let's be clear about this: there are places inside the United States of America that would be hard-pressed to accomplish all of these steps in 30 days; expecting such performance from countries with per capita health spending below $50/year is naïve in the extreme.

What, after all, is the incentive to report? If you were a poor farmer in southern Indonesia and suddenly half your chicken flock was sick, why is it in your interests to let anybody know about it? Even a wealthy livestock company in a G-8 nation might consider it "wise" to try limiting damage on its own, never reporting an outbreak. Unless governments have the clout to force notification, and can offer compensation to farmers that lack flock/herd insurance, this will always be the Achilles heel of animal surveillance.

Human disease surveillance systems are only as good as the public health infrastructure. SARS started in November 2002: the world officially learned of it five and a half months later. Ebola broke out in Kikwit, Zaire in January 1995: WHO was notified that samples of suspected Ebola-contaminated blood had been shipped to Belgium three months later. Even now human cases of H5N1 infection in Asia are being reported more than 80 days after they occur. Some of these lag- time issues are political (government cover-up; appointment of incompetent officials to crucial health positions; corruption), and it is difficult for representatives of an outside government or agency to confront them. But the real problem in most cases is *capacity*.

Last May, at the annual World Health Assembly, the 192 member nations debated pandemic flu policies and changes in the International Health Regulations (or IHR) for many days, with official arguments raging as late as 5am. Happily, the IHR were changed to a form that offers greater national transparency about disease and collective response to emerging threats. And the flu policy that was ultimately hammered out forms a good international legal framework of response. But throughout the long hours of debate the vast majority of nations repeated the same mantra, over and over: *we need resources*. That same mantra was heard this week in Geneva at the flu summit.

Wealthy country governments, the G-8, and the World Bank have long neglected the public health infrastructure problem. The HIV/AIDS pandemic has sapped systems that in many cases were barely functional to begin with. If the Africa flyway becomes contaminated with H5N1 (and it will, soon) we will see what happens when nonexistent public health infrastructures, enormous HIV+ populations, and a vast range of bird species meet H5N1.

In the long run we should view H5N1 as yet another warning shot across the bow for the wealthy world, signaling the need to invest heavily in development of public health

infrastructures in poor countries. But H5N1 may not give us time to create such infrastructures.

Short term "solutions" are obvious: bolster laboratory capacities, create standardized reporting mechanisms that are accessible to poor country residents, improve satellite and cell phone connections to allow rapid reporting of observations from all over the world. Syndromic surveillance is unlikely to be useful with flu, as the essential symptoms overlap with hundreds of other diseases, and the course of the illness in individuals is very rapid. Against a background of, for example, meningitis, malaria, HIV and TB, spotting high fevers due to flu could be impossible.

One immediate technological breakthrough that could make an enormous difference would be a rapid saliva-based dip stick assay specific for H5N1. It would look like litmus paper – lick it, it changes color, and we know you have H5N1. I am aware of several labs that are working on such a technology. The key will be finding manufacturers that are willing and able to manufacture hundreds of millions of these diagnostics at a price affordable to countries like Cambodia, Laos, Malawi and Ecuador.

The President's proposal and the HHS Plan released this week offer no specific allocations for development, manufacture and global distribution of specific rapid diagnostics. That is a tragic oversight. The plans also spend only 4 percent of the President's $7.1 billion request on improving the surveillance and response infrastructures in poor countries: That, too, is an oversight.

Last week the World Bank indicated it will put $500 million into the public health infrastructure effort, and the European Union this week promised to pony up $35 million. Combined, however, the $786 million promised by various wealthy-nation sources will not come close to meeting needs, especially if human-to-human transmissible H5N1 emerges in HIV-ravaged Africa.

- **Stop spread of influenza inside hospitals and medical facilities worldwide.** SARS is an order of magnitude less contagious than influenza, ultimately proving to be primarily a nosocomial disease. Such measures as quarantine, travel advisories and restrictions could succeed with SARS, but would have little, if ANY, efficacy in controlling spread of influenza. The most crucial lesson of SARS that would be applicable widely is that of hospital infection control. SARS spread primarily inside medical facilities, and comparisons of hospitals with very low levels of transmission (e.g. Queen Mary, Hong Kong or Bach Mai, Hanoi) to those with horribly high rates of in-hospital spread and death (e.g. Prince of Wales, HK) offers elegant and empirical proof of the efficacy of solid programs of infection control and patient isolation. Whether pandemic flu would prove open to mitigation through such means is doubtful, on a large scale, but individual lives and health care workers could well be saved by careful advance study and implementation of infection control measures. Further, epidemics have always spawned mass population migrations towards hospitals, particularly in poor areas, as desperate people search for solace, even if they are not themselves ill. The global paucity of such basics as soap, latex gloves, surgical masks, protective medical gowns, sterile syringes,

autoclaves, and portable generators to power sterilizers guarantees that hospitals the world over will be cauldrons of infection.

- **Managing to think, in a time of great uncertainty, on three planes at a time.** It is difficult for any leaders, whether in politics, industry, or nonprofit sectors, to create policies that address a given problem from three different event horizons all at the same time. But we have no choice with pandemic flu: it may emerge in a human-to-human transmissible form within 24 months, within 3-5 years, not for a full decade's time, or, if we are lucky, not at all. Investments and preparedness plans must consider the alarmingly slim list of options we have for action should H5N1 take on a rapid transmission form in the near future, but simultaneously we must invest in research and planning that may provide us with a far longer list of options for action in 2010, or 2015.

  In the past, federal plans (and local, State and international ones) tended to rest on overly optimistic assumptions about vaccine production and rather blithely ignored the vast chasms that exist in emergency response coordination and communications. Since the state of urgency over H5N1 escalated radically this summer, the weaknesses in past plans have become obvious to all.

  In the short term, then, planning must emphasize organizational issues, chains-of-command, international cooperation, melding of human health and veterinary efforts, supply problems for both anti-flu drugs (e.g. Tamiflu and Relenza) and a long list of general medications, hospital equipment, and even food.

  For a middle-term event horizon it is reasonable to expect that investments made today may result in vast improvements in diagnostics, vaccines, and perhaps even antivirals. Further, tabletop exercises, computer modeling, and a host of international efforts should provide planners with far more sophisticated understandings of the gaps and weaknesses in current systems of coordination and communication at all tiers, from the United Nations to city halls.

  And looking forward a decade it is reasonable to assume that a sound investment today in R&D will result in development and commercial production of a safe, effective universal flu vaccine that, with a single round of immunization, will protect individuals against all forms of influenza viruses to which they may be exposed in their lifetimes. Further, investments made today in ecological improvements in Asia – particularly China – could reasonably be expected to vastly decrease the probability of any given wild bird virus crossing to domestic animals and humans.

  The trick is to comprehend how budgets, at all levels from the UN on down, can appropriately reflect all three planes, all three event horizons.

- **Appreciate the limitations of current technologies, and understand that Tamiflu is not a terrific drug.** Several of the pandemic plans released by governments around the world, as well as the US plans released to date, rested heavily on the use of the anti-flu drug, Tamiflu. Made by Roche Pharmaceuticals in Switzerland, Tamiflu is not curative, but does slow down influenza viruses and offer patients some opportunity for a swifter

recovery. In addition, some studies indicate prophylactic use of Tamiflu reduces the chances that any given individual will become infected with circulating viruses. The later finding has prompted many governments to build pandemic control plans around various schemes of widespread Tamiflu use. In some iterations, the U.S. plan posited widespread prophylactic use of Tamiflu by first responders: Physicians, nurses, EMT personnel. It will be important to see which groups are targeted for Tamiflu use, and over what period of time.

While it is true that Tamiflu is the only drug we have, I hope that budgets will reflect recognition of the limitations of this drug and push for R&D aimed at replacing Tamiflu with far superior medications. Even in the short term I am anxious about Tamiflu.

The FDA has approved use in kids over 1 year of age for TREATMENT, but there is NO approved pediatric use for prophylaxis. (Yes, physicians can prescribe any drug for off-label purposes, but a national public health policy ought not rest on such flip use.) The public health model requires using Tamiflu on ALL humans in an exposed area to control spread. Worse, H5N1 seems to have been especially likely to target children so far, which means that any effective public health strategy for use of the compound would have to posit widespread distribution for prophylactic purposes to children of all ages. But there are no approved uses and no studies to guide decisions on the safety of giving Tamiflu (or Relenza) to kids who aren't already suffering flu.

Further, a manufacturer's warning was issued by Roche in 2003, based on rat studies: the extrapolation was that the babies and toddlers could have lethal effects from Tamiflu when taken correctly as treatment for flu. The manufacturer suggested (but offered no evidence) that the drug was crossing the blood/brain barrier in babies, and would cause lethal central nervous system effects. Roche therefore warned that no children under 1 year of age should ever take the drug.

Even in adults there are problems. Roche's own studies show that people who take Tamiflu suffer more nausea, vomiting, stomach pains and headaches than people given placebos --- and it is statistically significant. For example, twice as many Tamiflu users vs. placebo users suffered nausea; twice as many had vomiting; 1.5 times as many had diarrhea. (This may be a universal problem with neuraminidase inhibitors, as Relenza also produces nausea, vomiting, diarrhea and stomach pains in a sizeable subset of users.) Because of the way the data was presented it is not possible to discern whether these side effects are experienced in a small subset of users who have multiple problems with the drugs, or in a sizeable percentage of the drugs' users, each of whom experience one or two of the side effects. One prominent scientist who sat on the FDA's Tamiflu review panel recently told me, "You want to take Tamiflu? Prepare to be nauseated."

The side effects may not matter when an individual already has the flu, but in a prophylaxis context it may prove impossible to get mass compliance with these drugs over a sustained period. It is important to understand the compliance issue before making plans for large-scale, sustained use of the drug(s).

All prophylaxis studies have been done in adults -- none are pediatric, though some involve teenagers. They DO show efficacy, with 3 to 12-fold reductions in flu cases compared to placebo recipients (the variation in efficacy covers a wide range, depending on the study, however). That's good news. But given the drug appears to produce some "flu-like symptoms", such as nausea, vomiting and diarrhea, compliance with long term self-medication could be a problem. And, again, we have no pediatric data.

For Relenza we have data that shows it may reduce the length of flu illness by a mean of one day in infected kids. But the efficacy in kids under 6 years of age was so low that the manufacturer recommends it only for kids over 6. Here, too, there is no long term use data, though the inhalant drug is not really under consideration for prophylactic use.

Large pooled studies (metaanalyses contrasting the results of many separate studies) conclude that Tamiflu cuts the length of a flu episode by about one day in adults, and 0.9 days in children. Relenza's efficacy appears to be about the same. As prophylaxis, Tamiflu and Relenza appear to reduce the odds of coming down with flu by about 70-90% in adults.

BUT, the best such study (Cooper NJ et al, BMJ 326:June 7 2003; obtained on line) has this crucial statement: *"A lack of evidence exists for the use of neuraminidase inhibitors for preventing flu in children and in frail elderly people in residential care."*

A final consideration regarding pediatric use: metabolism. All studies indicate kids metabolize the drugs faster than adults, and this means direct mg/kg dosing comparatives are unwise. Though the drugs were eventually licensed for treatment of flu in kids, the scientific review panels argued about proper dosing, and were troubled by the direct mg/kg choice. The kids simply clear the drugs from their systems faster, meaning there is less available drug over time. In the end, the panel compromised and decided that the drugs were safe enough to warrant a blunt instrument approach to pediatric dosing.

Data submitted to the FDA by Roche shows a few other considerations:

- There was no statistically significant difference between placebo and Tamiflu in terms of delaying otitis media (ear infections) in kids, the most common outcome of bad bouts of flu. Since OM was the FDA-agreed measure of the efficacy of the drug for preventing serious forms of influenza illness, this has got to raise concerns about whether the drug worked. (In contrast, adult studies show marked reductions in bacterial pneumonia among older Tamiflu-users.)
- Pediatric use of Tamiflu was 8 times more likely to result in emergence of drug resistant forms of the virus, compared to adult use. (This could be related to the rapid metabolism issue in kids.) Kids who developed resistant viruses stayed sicker, longer on Tamiflu, thereby erasing the drug's benefit of, statistically, reducing the length of a bout of flu in kids by 0.9 days.
- This emergence of drug resistant mutants was quite troubling to the FDA panel. Keep in mind that a baseline survey of flu strains circulating worldwide in 2002-3 season found NO examples of resistance in nature to these drugs. So the possibility that pediatric use of the drugs promotes emergence of drug resistant

strains clearly worried the FDA panel. A crucial FDA review of the Roche data states:

> *"It also appeared that the mutant virus may be shed at high titers in some subjects before being cleared. Therefore, this reviewer has not been reassured that these viruses are harmless to the general population. The pediatric studies were not designed to determine if there was secondary spread of the mutant viruses to household or other contacts so there is no data regarding transmission of these viruses in vivo. Since these mutations involve the neuraminidase enzyme and to a lesser (but undefined) extent the hemagglutinin, there are also theoretical concerns that they could be antigenically distinct from wild type influenza. The review team believes that it will be of critical importance for the sponsor to further characterize these mutant viruses, the course of clinical disease associated with them, their potential for transmission in households and the nature of the antibody response to them compared to wild type influenza."* (NDA 21-087, NDA 21-246, June 2000.)

In reviewing all data on Tamiflu provided by the manufacturer as of March 2001, the FDA's Dr. Heidi Jolson, Director of Antiviral Drug Products, concluded:

> *"..once an individual contracts infection and develops influenza symptoms, the role of an antiviral appears to be limited. As demonstrated in the studies submitted in support of the applications for oseltamivir and zanamivir, early antiviral treatment results in only a modest attenuation of the course of clinical illness (approximately one-day shortening in the median duration of major symptoms with both products). Therefore, if promoted to the consumer, balanced promotion should contain information regarding the importance of vaccination, the reminder that not all viral illness is caused by influenza virus, and the likely modest treatment benefit a patient and healthcare provider elect to treat influenza with an antiviral medication.*
>
> *The clinical relevance of the modest treatment benefit is a highly subjective question.*
>
> *More definitive demonstration of clinical or public health relevance with the neuraminidase inhibitors will require additional data, such as studies to demonstrate prevention of influenza transmission or prophylaxis, reduction in influenza-associated complications or mortality, or the pharmacoeconomic gain due to illness shortening."*

In FDA hearings on February 24, 1999 regarding the licensing of the first of the neuraminidase inhibitors to reach the agency, Relenza, independent scientists were convinced that Relenza's efficacy was barely discernible in patients who simultaneously took over-the-counter drugs, such as aspirin and "flu medicines". Much of the debate among the review panel concerned how, exactly, the "efficacy" of the drug could be measured. Panel members were clearly skeptical that Relenza had much benefit, at all,

and some argued that the FDA and Glaxo had agreed on a set of clinical trial endpoints that ended up providing no real clarity. I have spoken to some members of that panel and they describe a great reluctance in the room to accept that the drug offered much, if any, benefit beyond what patients could obtain from the shelves of their local drug stores.

In the above metaanalyses that I referred to, this question of how many patients simultaneously took other flu medicines that they purchased at their neighborhood drug stores was not addressed. So we have no idea how profound a confounder over-the-counter drug use may be. It's possible Tamiflu and Relenza still have powerful impacts, beyond the OTC drug impacts. (Certainly, the adult prophylactic use benefit can be considered a genuine one, to be credited to Tamiflu, based on the studies' designs.) It is also possible that factoring for OTC drug use in the test subjects (both placebo groups and Tamiflu/Relenza recipients) would have revealed more problematic benefits from these pharmaceuticals, particularly in treatment for flu infections.

- **The Number One priority in the short term: Chain of command.** In any complex crisis the greatest failure is command, and its corollary, communication. In recent history only one American disaster witnessed a clear chain of command understanding, namely Rudolph Giuliani's clear leadership of 9/11/2001 responses. Conversely, lack of clear chain of command and communication was key to failures in New Orleans.

  Influenza pandemics are not singular events, such as the strike of a hurricane, the slip of an earthquake fault, or the suicidal attack by a terrorist. Rather, pandemics unfold over time, re-circulate in waves, continually mutate and persist for months, perhaps years. Planning must appreciate the difference between emergency response and long term disastrous outcomes, including shortages of food, medical supplies, essential products and business equipment. Chain-of-command for singular emergency events may differ from that which will be key to keeping societies functioning throughout a prolonged, horrible event.

  Few cities, states, provinces, agencies, or nations have thought this through and developed clear understandings of which individuals and agencies are in charge of the various facets of a pandemic response. We look forward to seeing clear delineation of these issues in the forthcoming multi-agency federal response plan for the United States.

- **Global and domestic responses must coordinate with nongovernmental and humanitarian organizations.** None of the plans presented to date at the international or national levels delineate roles for volunteers and nongovernmental groups, such as the Red Cross, Médecins Sans Frontiers (MSF), CARE, Oxfam, the Red Crescent, or WorldVision. No matter what assumptions are made about the expected numbers of infected and dying people in a flu pandemic the world lacks sufficient nurses, physicians, government first responders and employed officials to adequately respond. In some parts of the world the first warnings about new epidemics and disease emergences have come from humanitarian groups, particularly MSF. It is imperative that governments work closely, at all tiers, with private volunteer organizations to coordinate recognition, surveillance, and response efforts. Such groups must be considered *partners*, not mere adjuncts, in a global effort.

- **The role of the military and national security response is complex and requires considerable forethought.** In the U.S. we face a unique problem, born from our engagement in Iraq. In order to avoid a divisive military draft, the Bush Administration ordered the Army Reserves and National Guard into foreign combat. Among other things, this has blurred the lines between the various armed forces in America and left us bereft of National Guard under individual states' control for response to domestic crises. The weakening of the National Guard was an apparent problem following Hurricane Katrina and will continue to be a special issue for the U.S.

  Historically, the lines between the National Guard and U.S. Army, Air Force, Navy, and Marines were far clearer, and it was entirely appropriate to posit a role for the National Guard in a pandemic response. That is no longer the case.

  Internationally, the nature of State response to this issue will vary dramatically. Some countries routinely use their armed forces for police actions and probably will not hesitate to do the same in a pandemic. The opposite may also be true: when I was in the Ebola epidemic in Zaire in 1995 the army fled the region, leaving the people to fend for themselves for several weeks.

  You might well ask this question: if a nation has an adult HIV prevalence of 35%, and the effect of HIV on H5N1 infection is to double the flu mortality rate, what will happen to the forces of State security? If a nation is fighting wars on two fronts involving more than 200,000 troops, and H5N1 turns out to mirror the 1918 flu in that it takes its highest toll among young adults, how can the armies continue to carry out their operations? If, in addition, their enemy practices suicide bombings, and therefore cares not whether it is infected with a deadly virus, how might the pandemic affect the course of the wars?

  The armed forces of the U.S., Canada, France and dozens of other nations are among the best organized forces for rapid deployment, transport, and infrastructural support. There is more to modern militaries than shooting guns and dropping bombs. Just ask the people of Aceh: who got there first, after the tsunami? I'll give you a hint – it was a navy with red-white-and-blue flags flying. Why? Because making one's way thru newly reshaped reefs and shoals, with entire coastlines utterly re-mapped, to deliver supplies for hundreds of thousands of people required a modern satellite-guided naval armada.

  While I strongly support the use of U.S. military personnel for logistics, supply and support activities, both domestically and overseas, in response to a flu pandemic, I do not believe the Army, Navy, Air Force or Marines ought to be considered primary enforcers of domestic quarantines or public health actions.

- **A final note……**There are at this moment unconfirmed reports of H5N1 die-offs among bird populations in Iran and Iraq. If true, these could foretell spread of the virus to the African flyway, which would include a spectacular range of species migrating from Ethiopia to South Africa. We do not know how H5N1 will behave in the body of an HIV+ human being. There are two theories, scientific rationales for which are a bit too

complicated to detail here. Nevertheless, in one scenario the HIV-weakened immune systems of infected individuals create permissive environments for H5N1, allowing the flu virus to thrive, mutate and adapt to human beings. In such a scenario, the HIV+ person is, in a sense, an ambulatory Petri dish, incubating, and possibly spreading, new forms of the virus.

In a second scenario, however, the HIV+ individual, unable to mount a protective immune response against H5N1 is easily infected and swiftly devastated. In that situation vast populations of HIV+ people could be obliterated by the pandemic flu. This is a horrible notion, and ominous given the extraordinary HIV infection rates in many African countries.

Regardless of which HIV/H5N1 scenario is correct, spotting any movement of the flu virus from African birds to the continent's peoples will be exceedingly difficult. As weak as the public health infrastructures and surveillance systems are in much of Asia, such capacities are far worse in sub-Saharan Africa. Further, spotting symptoms such as the emergence of clusters of people with high fevers and nausea might be impossible against a background of malaria, tuberculosis and HIV.

It is imperative that the international cooperation components of the forthcoming multi-agency U.S. pandemic plan will give close attention not only to improving surveillance and response capacities in Asia, but also in Africa.