Setting the Stage

Most of the problems jeopardizing our national security today have answers; we just don’t always know how to get to those answers. For example, we know that to contain the nuclear threat we need to secure all of the existing fissile material and prevent the creation of nuclear fuel-enriching facilities; we just don’t currently have the capital—monetary or political—to do it right now. But then there are problems entirely devoid of solutions either because we have yet to conceive of how to accurately approach them or we simply haven’t had the imagination to reconcile the dilemmas they create.

Biological threats fall into this unappetizing category of unanswered problems. Of all the weapons of mass destruction (WMD), biological agents have been around the longest, and we are no closer to eliminating them than we were a thousand years ago. We may be less likely today to die from specific agents like smallpox or polio, but the overall threat of new diseases emerging is no less than it has ever been. The diseases that these agents create have threatened mankind since before civilization existed, and the more complex and interconnected society gets, the more vulnerable it becomes. Terrorists can’t create hurricanes and Mother Nature doesn’t build nuclear weapons, but biological events have the macabre distinction of spanning both realms.

Only five years old, the 21st century has already been a bountiful testing-ground for the disaster community. September 11th dramatically brought terrorism—and with it disasters—to the forefront of the American psyche. Its aftermath inspired the creation of the Department of Homeland Security along with some serious self-reflection in both the intelligence and disaster communities. A few weeks later anthrax reminded us of ancient biological threats, and two years after that SARS introduced a novel one. In the past year alone tsunamis and earthquakes have struck all corners of the world, reminding us of the logistical hurdles inherent in any disaster response. Most recently, hurricanes have pounded both the US coastline and our confidence that much has really changed with all of the reforms in the disaster community.

The response to Hurricane Katrina failed because authorities didn’t appreciate advance warnings and were unable to quickly adapt response capabilities when the levees gave way. Today a much more complex and potentially devastating threat is looming, and instead of hours to days, we have months to years worth of warning. The H5N1 strain of Influenza A is brewing in Southeast Asia, along with other potential culprits, and we may discover eventually that the index case for the United States is already here.

With a global pandemic waiting in the wings, what is preventing us from really preparing for it? Perhaps we aren’t convinced that the threat is real, or we think it is too far away. Maybe the cost of preparing is prohibitive, and we believe it would be less expensive to clean up the mess in a particular location afterwards rather than prepare everywhere beforehand. Or, more likely, we’re just not sure what exactly needs to be done. The new HHS Pandemic Influenza Plan released on November 2, 2005, is not the kind of answer we are looking for.2

Losing lives isn’t the whole problem, and stockpiling Tamiflu isn’t the whole answer. So what is? This is a paper about asking the right questions, defining
the real problems, and appreciating their implications. This paper will communicate the urgency, provide a greater understanding of what is at stake, and, in doing so, lay the groundwork for real solutions. It is designed to give some very difficult answers to some very simple questions and ultimately move us closer to answering: how do we respond to a threat with infinite potential without infinite resources?

WHAT DOES BIO REALLY MEAN?

All disasters are not created equal. They can be small or large, and they can be short or long, as shown in Table 1.

The size element relates directly to the amount of response resources required. While the specific geographic distribution is significant, it is simply a question of supply versus demand. The time issue, however, is far more complex. On September 11, 2001, the first plane hit the north tower of the World Trade Center at 8:45 AM. By 10:30 AM both towers had collapsed, and the event was over. It was only a recovery mission after that.

If an explosion is a photograph, then a pandemic is a movie, and the camera starts rolling before we even realize that a disaster is unfolding. It will begin quietly with a single person anywhere in the country—or the world—who gets infected but shows no symptoms for two to 14 days, during which time the individual can cross any border undetected and even infect others while asymptomatic. When it finally presents in the form of a sick patient, it will look like any other seasonal flu, so no suspicion will be aroused. A slew of differential diagnoses will be posited before the real diagnosis is made, and many others will be infected during the process. If a train derails in the countryside, responders must be sent to the crash site. A pandemic, on the other hand, comes to the healthcare system. In fact, it walks in the door.

A pandemic is a story that grows more complex with every new infection. It is a dynamic process that begins at one end of the world and flies to the other in a matter of hours. Unlike any other disaster, a pandemic will continue to grow exponentially until it is stopped or it burns itself out like a forest fire, but people are destroyed, not trees. But after the Black Plague had "burned out" in the 14th century, one quarter of Europe's population was gone. A biological event is also different from all other events because citizens themselves become threats, and this greatly complicates the policy decisions. When citizens become weapons, self-defense becomes self-mutilation, and the requisite decisions are politically unsavory.

When we think of WMDs, we think of states or terrorists who wish to harm the United States' citizens and redirect its foreign policy. We assume a human actor with a purpose, but while nuclear and chemical attacks must be orchestrated, biological attacks can just happen. Pandemics are Mother Nature's WMDs, and while the term has become popularized recently, the relevant issue is more disruption than destruction. Destruction is harder to create, geographically limited, and easy to clean up. Disruption, on the other hand, is very easy to create, can expand indefinitely, and drains numerous resources. Destroying every gas station in the country is hard to do; driving up the price of gas at all of those facilities is not. In a platoon of soldiers diarrhea is worse than death. While in either scenario a soldier's performance is lost, in the former more resources are required. Put simply, a dead soldier is a loss of one; a wounded soldier is a loss of up to six or seven: one wounded and the others to rescue him. In a pandemic, a million deaths is less disruptive than a million sick people and 10 million "worried well."

Disasters result in three types of impact: casualties, terror, and economic damage. While all three are interrelated, it is important to divorce the concept of strategic significance from numbers of casualties. The media likes to focus on casualties, but our reaction to death varies widely by context. Over 42,000 people

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### Numbers tell the truth

| 6-8 months | Time required to manufacture a new vaccine. |
| 25 million | Number killed worldwide in first six months of the 1918 flu pandemic. |
| 48 hours   | Time after onset of flu symptoms that Tamiflu must be administered. |
| 13.5 days  | The mean time it took to collect specimens to diagnose SARS in Hong Kong. |

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died in motor vehicle accidents last year, but no one drives any slower. When five people died from inhalational anthrax in 2001, however, thousands of people consulted their physicians and everyone started stockpiling Cipro. So when we talk about the 1918 flu pandemic killing more than 500,000 Americans, bear in mind that we lose 2.5 million people every year and life goes on. Death is undoubtedly tragic, but it can be ignored, or interpreted, or rationalized. The economy, however, is what holds the country together. Eliminate the American economy and 300 million people would be affected, and the entire world economy would waver. Suddenly, we are out of the tragedy realm and into the strategic “Fall of the Roman Empire” arena. It took Europe hundreds of years to recover from the Black Plague. Irreversibly crippling the US economic base could change the global balance of power, and this is no secret to our enemies.

**WILL IT HAPPEN?**

The simple answer is: probably! Capitol Hill, however, is not so dichotomous. When decisions of policy and funding are made, everything must be qualified and quantified. The poignant question is: when will it happen? Without a crystal ball at our disposal, we are left with applying a clear understanding of what is happening right now to our experience from the past.

It could happen soon. Threat assessments calculate potential impact from a given threat by taking into account three things: 1) our vulnerability, 2) the likelihood of a threat, and 3) the consequences of that threat being visited on our nation. An exact likelihood is difficult to calculate, but with consequences potentially so great, even a remote likelihood should prompt earnest preparations.

It has happened before. Influenza pandemics have traversed the globe on four occasions in the last 150 years: 1890, 1918, 1957, and 1968. The most devastating—and thus most memorable—was the 1918 “Spanish Flu,” which killed more people in 24 weeks than AIDS has killed in 24 years and ultimately killed three times as many people as the Black Plague. Even the coincident carnage in the trenches of WWI paled in comparison.

While new research in molecular genetics has shed some light on the origins of the 1918 H1N1 strain of influenza, we still don’t have a clear understanding of why it appeared so quickly, why it disappeared just as quickly, and why it left so many dead in its wake. Without that understanding, we are left to assume that an equally or more deadly virus may appear at any moment. The potential of biology has not changed significantly in the last 100 years, but the environment in which it operates has. So, how has the world changed since 1918? Can we assume that healthcare has improved? Surely advances have been made, but are they relevant? Undoubtedly our ability to provide supportive respiratory care has improved, and we have a myriad of antibiotics for secondary bacterial infections. Our progress in the world of viruses, however, has been much less significant. And while we have vaccines and antivirals, the real question is: will they work?

If they don’t work, and they may not for reasons discussed later, then not much in healthcare has effectively changed. The global transportation system, however, has changed significantly. The 1918 flu circled the globe several times in 18 months, and commercial air travel didn’t even exist yet. Recently, SARS traveled from Hong Kong to Toronto in a matter of hours. Advances in healthcare, including some cancer and autoimmune

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**Ten common misconceptions regarding the threat of avian flu**

1. We know when it will happen.
2. We know why it will happen.
3. We know what will happen.
4. We know how to stop it.
5. We have a plan.
6. We are better off than we were in 1918.
7. Pandemics aren’t such a threat: look at SARS.
8. We have vaccines and antiviral drugs that we know will work.
9. Investing in flu vaccine is a waste of money if a pandemic never happens.
10. We know basic things like why the flu comes in winter.

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Journal of Emergency Management  
Vol. 4, No. 1, January/February 2006
therapies, along with AIDS, have created a much larger, vulnerable population of immunocompromised people. Finally, whether or not American society has become less inclined to collectively mobilize for such an event—because of a further cultural fragmentation and growing distrust of the government—is a distinct possibility. So too is the willingness of the American people to forgo their mobility, temporarily, as part of quarantine.

How do we know it will happen? Anyone who has wandered through a chicken market in rural Southeast Asia can appreciate the challenge inherent in preventing the jump from birds to humans. In order to believe that we will never be threatened, we must be confident in one of two facts: 1) that the global healthcare system is strong enough all over the world to prevent an attack from occurring, or 2) that our domestic response system is pervasive and agile enough to handle any outbreak after it has started. We talk about containing an outbreak as if it were a one-time occurrence. Unlike disrupting a terrorist cell with aspirations to build a nuclear device, stopping one pandemic does not make it any less likely that another will occur—especially if the infection organism resides in an animal reservoir. Yet, of the $7.1 billion requested of Congress for the influenza plan, only $250 million is allocated to assist foreign countries in improving their disease detection and surveillance systems.

As of November 2005, the World Health Organization (WHO) has declared that we are currently in the third stage of the six stages of a pandemic, which puts us at the beginning of the Pandemic Alert Stage. This means that a new virus strain has been identified in humans, but we have yet to see any human-to-human transmission. Human cases of avian flu have been officially confirmed in five countries: Indonesia, Vietnam, Thailand, Cambodia, and China. Cases in birds, however, extend from Japan to Croatia and include 16 countries along the way. It is impossible to know how many cases have yet to be identified or which one will be the tipping point. Most likely, human-to-human transmission has already occurred somewhere and has just yet to make itself known. This is not to say that the pandemic has already started; any pandemic probably has a number of false starts that are never identified. But the seasonal trend over the last few years is ominous.

**WHAT IS PROTECTING US NOW?**

The history of our national disaster response system is an alphabet soup of undulating acronyms, consolidating and dispersing in endless cycles like so many universes expanding and contracting. But it is still useful to examine the motivation behind the creation of successive organizations to understand the capabilities and limitations of our current system. In short: the main reason our existing disaster response system is not very well equipped to handle a biological disaster is that it was never designed for one.

Two hundred years after its founding, the United States did not have a singular federal organization in charge of disasters. The 1960s and 1970s were punctuated by a series of earthquakes and hurricanes across the country that highlighted the need for such a central body. The pivotal moment, however, came in 1978 when the Department of Defense (DOD) staged a classified worldwide deployment exercise called Nifty Nugget. The results were disastrous. Had the exercise been an actual conflict there would have been 400,000 troop casualties, and between 200,000 and 500,000 trained combat troops would not have arrived at the combat zone on time.4

Appreciating the logistical nightmare, the following year the military created the Joint Deployment Agency and would later form USTRANSCOM to coordinate multimodal—air, sea, and land—transportation. On the civilian side, President Carter created the Federal Emergency Management Agency (FEMA) to consolidate disaster-related responsibilities from a number of disparate organizations. (FEMA assumed responsibilities from the Federal Insurance Administration, the National Fire Prevention and Control Administration, the National Weather Service Community Preparedness Program, the Federal Preparedness Agency of the General Services Administration, and the Federal Disaster Assistance Administration from the Department of Housing and Urban Development.)
Three years later President Reagan formed the Emergency Mobilization Preparedness Board, and its recommendations became part of National Security Decision Directive 47, which created the National Disaster Medical System (NDMS). The NDMS was originally conceived as a joint venture between the Department of Health and Human Services (HHS), the DOD, FEMA, and the Veterans Affairs (VA) hospital system. In the event of a disaster, HHS would provide medical supervision, DOD would provide transportation to evacuate casualties, VA would provide hospital beds to receive the casualties, and FEMA would oversee the whole process and help pay for the aftermath. In addition, Disaster Medical Assistance Teams (DMATs) were created to provide mobile teams of emergency medical professionals that could be deployed to a disaster site and be self-sustaining for 72 hours.

Originally designed for nuclear attacks, FEMA was heavily criticized for its response to Hurricane Hugo in 1989 and Hurricane Andrew three years later. It was accused of bureaucratic delay and became known as a political dumping ground for friends of the president. In the mid-1990s, reforms were able to streamline the organization, and it received much praise after its response to the Oklahoma City bombing in 1993. But, after September 11, 2001, FEMA was swallowed by the newly created Department of Homeland Security (DHS) and its focus shifted to terrorism. In 2004 the National Incident Management System (NIMS) was created, and the National Response Plan (NRP) was drafted to consolidate pieces of a number of competing plans. (The NRP primarily replaced the Initial NRP [INRP], the Federal Response Plan [FRP], the US Government Domestic Terrorism Concept of Operations Plan [CONPLAN], and the Federal Radiological Emergency Response Plan [FRERP].) Apparently, these reforms were a step backwards because a year later, after Hurricane Katrina, FEMA was once again accused of bureaucratic delay, and its leader, Michael Brown, was castigated as a political friend of the president with no disaster management experience.

There are three phases to disaster response: 1) prevention, 2) mitigation, and 3) relief. FEMA is primarily designed for disaster relief: what happens after the disaster is over? It is very effective as a mechanism for distributing federal loans and grants to help rebuild an area after a disaster, but its ability to mobilize resources during a crisis has repeatedly come into question. The
main difference between disaster relief and disaster mitigation is the time element, and time is the defining feature of a biological disaster event.

Katrina demonstrated how difficult it is to respond to a hurricane even after decades of similar events, and yet a biological event is much more complex. Katrina had a few days worth of warning; a nuclear strike would have little or no warning but would be obvious enough once it happened. A bio attack, on the other hand, would already be well underway—probably for a few weeks—before being detected. While the mass evacuation for Hurricane Katrina proved problematic, a complex evacuation is much simpler than the opposite: not being allowed to evacuate anyone at all. An evacuation is a luxury compared to a quarantine because most of the people want to leave, and you know when everyone’s out of harm’s way. A bio event can be in multiple locations at once, and new cases can spread as quickly as modern transportation. The disaster enters the healthcare system without warning or control and starts pulling society apart at the seams.

On a broader and more worrisome level, the history of disaster response reveals a reactive culture: the tendency to plan for a disaster after it has already happened. The only thing worse than no plan is a plan that we think will work. The National Pandemic Influenza Strategy was released on November 1, 2005, and the HHS Pandemic Influenza Plan appeared the following day. Health officials began drafting the plan back in 1991, and 14 years later it still is not clear who is in charge of a pandemic response. It emphasizes stockpiling antiviral drugs, assuming they will be effective, and developing vaccines, assuming they will be available in time. It talks about restrictive movement, but if policymakers hesitated to admit that we had SARS cases in the United States and failed to evacuate most of New Orleans because of the feared economic impact, what makes us believe they will have the political clout to declare a widespread quarantine? Ultimately, the plan defers most of the responsibility to the state and local governments, ensuring that more time will be spent quibbling over funding than actually preparing.

Every disaster after-action report has the same complaints: lack of clear leadership, poor inter-agency communication and coordination, bureaucratic delay, inadequate infrastructure or loss thereof, and insufficient surge-capacity. New plans always say that they are going to fix those problems, but they never explain how at the operational level. We are currently being protected by fantasy plans: the kind that sit on shelves as “symbols of control, order, and stability. These ‘fantasy documents’ attempt to inspire confidence in organizations, but they are disturbing persuasions, soothing our perception that we ultimately cannot control our own technological advances.” What is a plan anyway? It’s a promise about what will happen. If you could really plan for a disaster, then it wouldn’t be a disaster.

WHAT HAVE WE LEARNED?

Skeptical policymakers often cite what SARS wasn’t. It only killed 774 people worldwide, and there was no human-to-human transmission within the United States. But how about what SARS was? SARS was a wake-up call to the global community about the emergence of novel biological agents, and it provided a brilliant in vivo experiment to demonstrate the spread throughout the world of a pathogen for which we have neither vaccine nor treatment. A map alone is sobering: in a matter of months, SARS traversed the entire globe and hit predominantly industrialized nations. The more well connected a country was to the international transportation grid, the more likely it was to be affected. Countries fared differently, however, based on their response strategies. After China, two of the hardest hit countries were Canada and Vietnam. A look at their different experiences reveal, somewhat counter-intuitively, how a very industrialized country with a first-rate healthcare system can fair far worse than a country with comparatively limited resources.

The outbreaks in both Toronto and Hanoi began at the same time in essentially the same way: each city received a single index case of SARS during the last week of February 2003. But from there the responses in each country differed in a number of important ways. In Canada a “Code Orange,” which requires all hospitals to go into emergency mode, was not declared until 30 days after the first SARS case. Vietnam, in contrast, began preparations for a SARS outbreak months before the first case arrived. Back in December of 2002, the Vietnamese Ministry of Health had distributed the “Ten
Measures for Prevention Against SARS to hospitals around the country. In Canada, clear recommendations and uniform guidelines were not given to healthcare workers until the outbreak was well underway. The first case to present to Toronto’s Scarborough Grace Hospital on March 7th was the son of the index case, and he spent 18 to 20 hours in the ER where first pneumonia and then tuberculosis were suspected before SARS. In Canada, SARS patients stayed where they presented and ended up in 20 different hospitals at once. Early on Vietnam designated two SARS hospitals: the French Hospital of Hanoi and the Tropical Medicine Institute at the Bach Mai Hospital in Hanoi. Neither hospital in Vietnam had negative pressure isolation rooms, while many of the facilities in Toronto did. Individuals exposed to infected persons in Canada were asked to stay in their homes and were loosely monitored, while such individuals in Vietnam were quarantined in specific facilities. After months of screening at airports, Canada never quarantined any travelers, but Vietnam quarantined thousands and even quarantined 2,000 Vietnamese students at once who were evacuated from China. Canada followed the WHO guidelines for discharging patients and generally quarantined contacts for 10 days. Vietnam, on the other hand, exceeded the WHO requirements for giving SARS patients a clean bill of health and generally quarantined contacts for up to 14 days. Healthcare workers constituted 40 percent of the SARS cases in Canada, while healthcare workers constituted 57 percent of the cases in Vietnam. On April 28th, 2003, Vietnam declared their SARS outbreak over. All in all, 68 cases were recorded and SARS was never heard from again. On May 17, 2003, Canada declared its SARS outbreak over. By then Canada had 372 cases, and a second outbreak after the declaration would affect 66 more patients.

In the end, some fortuitous measures and a little practical ingenuity contributed to Vietnam’s success. For example, because the Bach Mai Hospital did not have sophisticated negative pressure rooms for SARS patients, they did something unheard of in other countries: they opened the windows. Bach Mai is one of the few hospitals that did not have a single healthcare worker infection.

In addition to historical lessons, simulations can provide some insight into the efficacy of different response strategies. A group at the Los Alamos National Laboratory adapted a computer model of traffic patterns in Portland, Oregon, for a smallpox outbreak named EpiSims. Historically, most simulations either assumed a simple geographic spread like the Black Plague as it moved across Europe in the 14th century, or they made simple, uniform social networks. EpiSims modeled a realistic small-world network with complex connections and so-called “super-spreaders.” The model ran a number of scenarios: 1) no intervention, 2) ring vaccination, and 3) total vaccination. It ran each intervention at different times: after a few days or after a few weeks. The simulation found that regardless of what intervention was done, the most important element was time. It also discovered that social distance strategies—like shutting down gathering places such as schools—was almost as effective and more timely than vaccinating everyone. The bottom-line was—a faster response meant fewer casualties. Another simulation modeling an outbreak of influenza in Thailand came to the same conclusion.
WHAT ARE WE UP AGAINST?

First, a quick biology lesson for the uninitiated. Influenza—from the Orthomyxoviridae family—comes in three forms: A, B, and C, and a typical viral particle ranges from 80 to 120nm. Influenza C causes very little morbidity and is generally disregarded. Both A and B contribute to the endemic flu that traverses the globe every year, but only A infects species other than humans, which complicates matters. Influenza A is further classified based on two surface proteins: Hemagglutinin (H) and Neuraminidase (N) like the current threat “H5N1.” H is involved in viral binding to host cells, and because it is an important antigen for the immune system to recognize it, is a critical part of the flu vaccine. N is involved in the budding of newly manufactured viral particles from host cells. It is also an important component of the flu vaccine and is the target of the popular antiviral drugs Tamiflu and Relenza.

What makes influenza both fascinating and problematic is its uncanny ability to mutate. The reason a new flu vaccine must be manufactured every year is that the virus mutates during its journey around the world every year. For the 2005-6 flu season, for example, the Vaccines and Related Biological Products Advisory Committee of the FDA met on February 16-17, 2005, to decide which strains of flu that were collected from laboratories around the world should be included in the following year’s vaccine. It’s an educated guess that usually includes two As and one B. The 2005-6 cocktail includes: A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2), and B/Shanghai/361/2002.

The virus has two mutation mechanisms: genetic drift and genetic shift. Genetic drift is the gradual point mutation of ribonucleic acids during viral replication that causes subtle changes in the viral population over time. This propensity was beautifully illustrated in a Nature article where “large-scale sequencing of human influenza [revealed] the dynamic nature of viral genome evolution.” The second, and potentially more devastating method of mutation, capitalizes on the fact that the Influenza A genome consists of eight single-stranded negative sense RNA molecules. Genetic shift is the sudden change in the viral genome when two viruses—often infecting the same host simultaneously—actually swap whole RNA segments, allowing viruses to exchange not just simple mutations but whole functions en masse. The classic, feared scenario is a high mortality strain that can only infect birds crossing with a low-mortality strain that can only infect humans to create a high-mortality human strain. These various mutation mechanisms also allow the virus to become resistant to antiviral drugs and render vaccines ineffective.

Besides a history of pandemics, influenza is more feared than other agents like SARS because of what we see the endemic strains do annually. Every year the flu circles the globe and blankets the entire United States in about eight weeks. Every year the flu kills about 36,000 people in the United States, which is about four times as many as AIDS. Worldwide, between 250,000 and 500,000 people die of the flu annually. Compare that to the scare SARS made with 774 deaths. Granted, most of the people who die of flu are either very young or very old—for everyone else it is merely a nuisance. But that is precisely what makes H5N1 so frightening.

The first human case of H5N1 was identified in Hong Kong in 1997, and it has been reemerging during the winter ever since. In 2003 human cases appeared again in Hong Kong and also in China. In 2004 it was identified in Thailand and Vietnam. In 2005 it is currently in Thailand, Vietnam, Cambodia, Indonesia, and China. During these outbreaks, the mortality rate has hovered around 50 percent (as of November 14, 2005, there have been 126 human cases of H5N1 with 64 deaths documented since December 2003), and most of the deaths have been of people under the age of 40. This is precisely what set the 1918 flu apart and made it so devastating. The Spanish Flu had the highest mortality for the 20 to 40-year-old age group and nobody knows exactly why. Perhaps a similar organism had passed through 40 years earlier and provided some protection to the older population, but the records aren’t specific enough that far back. Perhaps World War I, which was unfolding simultaneously, packed 20-year-old soldiers into crowded living conditions and paraded them around the world. Or perhaps it was something inherent to the virus. New research suggests that...
H5N1 creates an immune storm which may, in part, account for the age distribution of deaths. We don’t know for sure, but we can see it happening again today.

Right now, regarding H5N1, the “Avian Flu,” here’s what we do know. Unlike the viruses that caused the flu pandemics of 1957 and 1968, which arose when human and avian flu viruses infected the same person at the same time, allowing their genes to mix, recent genetic analysis suggests that the 1918 H1N1 virus came directly from birds.11,12 A closer look at the H5N1 genome reveals that it is currently only a few mutations away from looking like H1N1.12 Looking at the three RNA polymerase genes, only 10 amino acids consistently distinguish avian influenza strains from the 1918 H1N1 strain. Of those 10, four of the mutations have been identified in H5N1 strains, although not all in the same strain. Variations of the other six mutations have been identified in other avian flu strains like H7N7. It would appear that H5N1 is mutating to appear more and more like its deadly cousin H1N1.

At the same time, there are still some important facts about H5N1 that we don’t know—some of which we will never know. We still don’t know exactly which mutations are necessary to make H5N1 able to transmit from human-to-human in a deadly form. We don’t know what mutations are actually happening right now in the H5N1 population, and we don’t know where exactly they are happening. Given what we know about biology, it is likely that the necessary mutations have already happened in a bird somewhere, and it may have already jumped to a human. Suffice to say it will. But luckily there are still a few steps between the killer bug materializing in a bird and a worldwide pandemic.

WHAT TOOLS DO WE HAVE?

The current HHS Pandemic Influenza Plan focuses a lot of attention on current countermeasures, so it is worth exploring what our options are at the moment. The goal of any intervention is to disrupt the fundamental SIR epidemic cycle depicted in Figure 1.

For example, vaccines and isolation prevent infection; antiviral drugs hasten recovery. Table 2 categorizes the tools available to us as of November 2005.

Agent specific countermeasures are logistically convenient because they are “fire-and-forget.” A vaccine is a one-time shot that provides immunity thereafter. Project BioShield has spent a lot of time focused on these types of countermeasures. Unfortunately, agent-specific tools must be individualized and some biological agents are moving targets. Already strains of H5N1 have appeared in Vietnam that are resistant to the antiviral of choice: Tamiflu. Tamiflu, which inhibits neuraminidase, must be given within 48 hours of the onset of symptoms, which presents an additional logistical challenge. At the moment, the drug is only manufactured by one Swiss company, Roche, although negotiations are underway for the production of a generic version. In the meantime, with governments stockpiling the drug around the world, major shortages already exist. The drug is also produced from star anise, which is only found in southern China and is in limited supply. Other production methods are currently under investigation. The second-line drug is Relenza, but not enough meaningful data about its use with H5N1 has been collected.

The National Institute of Allergy and Infectious Disease (NIAID) began development of a vaccine for H5N1 in April of 2005, as have a number of groups in China. Early trials show some success although higher doses than expected have been required, which raises production concerns. The vaccine business in general is not a popular one, given the financial incentives (or lack thereof), which is why only a few companies manufacture the vaccine for endemic influenza every year. The fragility of the system was demonstrated by massive shortages last year when...
one of Chiron’s plants was shut down. The current method of vaccine production—developed in the 18th century—uses chicken eggs to produce inactivated virus and requires six to eight months of production time. If the mutations required to allow H5N1 to jump from human-to-human also rendered current vaccines ineffective, then a new vaccine would be a long time coming. New techniques using gold-bonded DNA vaccines are being explored but are not at the scale required for serious production. The one logistical benefit of vaccines is that not everyone need be inoculated. A sufficient percentage of the population, known as “herd immunity,” would be sufficient to prevent the propagation of an epidemic. Also, there is some inherent immunity in any population, which is why most of Europe survived the Black Plague, and even a few people with certain mutations are immune to AIDS, but it’s usually not a significant number of people.

The nonspecific countermeasures will work against any threat, but they tend to require constant vigilance. Hospitals with infectious agents employ airborne precautions for a variety of ailments in the form of masks, gowns, and negative pressure rooms. Isolation of sick people and quarantine of contacts is also key to any response. Social distance management is one of the simplest measures, and it involves both the ubiquitous wearing of masks (as in East Asia during the SARS epidemic) and the closing of public spaces like schools and stadiums. The problem with quarantine is the economic impact. We call it the “host response” phenomenon: when the response to the threat, rather than the original threat itself, kills the organism, as in the case of septic shock. This is why politicians hesitate to close borders; it’s a nasty position to be in: to accept casualties or to accept massive economic damage. Neither is a very pleasant choice.

Research into future options includes nonspecific immune system enhancement of the population and competitors. A competitor, which does not yet exist, is similar to a live, attenuated vaccine like the Sabin polio vaccine. A competitor, however, would readily infect a population—jumping from person to person—without causing disease in order to confer immunity to a more deadly cousin. The rationale is that the only thing that travels through a population as quickly as a virus is another virus, so it would be the equivalent of a self-propagating rapid vaccine distribution that only requires a few initial doses.

**WHAT NEEDS TO BE DONE?**

There are two obvious solutions: 1) slap masks on everyone in society at all times, or 2) reconfigure society so that all communication is telecommunication and human contact is eliminated. For obvious reasons, neither of these solutions is very appealing. So what are we left with?

The summer of 2000 was one of the toughest seasons for fire fighting in the United States in years. Over 122,000 fires burned over 8.4 million acres of land. In July, local crews in Montana were overwhelmed, so the National Interagency Fire Center called upon resources from all over. All told, more than 30,000 people, including civilian firefighters, state personnel, National Guard, Army, Marines, rural fire department personnel, and people from countries outside the United States, including Canadians, Australians, New Zealanders, and Mexicans, were on fire lines or filling overhead positions. Why can’t our healthcare system respond to a growing disaster so quickly with a multinational coalition including multiple branches of the military?

The main question is—can we evolve the current NDMS, or does it require a total revolution? The system
can’t be changed overnight, so what can we do now? Clearly, the old NDMS doctrine of evacuation needs to be updated to include quarantine. When to quarantine is the biggest question. The probable SARS case estimate in the United States fluctuated from 344 to 27, but whatever it was, it wasn’t enough to institute widespread quarantines. But how many would have been enough? How to quarantine is another question. Negative incentives, like bringing in the military to help contain people, should be augmented with positive incentives, like providing the best healthcare available in the hot zone. And, finally, once quarantine is established, then what? How do resources still move quickly in and out of the area? It has been estimated that if the bridges around Manhattan were all closed at once, the supermarkets on the island would have empty shelves in a matter of days. Such just-in-time supply models are typical of most hospitals as well. Quarantining people in their homes is also a quick and simple measure, assuming we can still provide the necessary services. A telemedicine system in conjunction with robotics, however, would be able to operate through and within a quarantine border, and we explore this concept further in other papers.15

Right now we can distribute masks, and other social distance strategies can be implemented in the event of a pandemic fairly easily, like closing schools and other gathering places. Vaccines and antiviral medications can be stockpiled but not at the expense of other more assured strategies. We can also invest more in combating the issue at its source in Southeast Asia with increased epidemiological monitoring and compensation of bird farmers, but, again, these are only temporizing measures. Regardless of what strategies are currently being proposed, the environment in which they are going to be implemented must be considered. Some measures that are doable in the intermediate future are impossible in the urban community and maybe even unnecessary (because of social distance) in the truly rural system, particularly if it is someplace like northern Maine, or even Vermont’s Northeast Kingdom. Distributing a medication within 24 hours, for example, would be an impossibility in New York City but quite feasible in Burlington, Vermont. If the whole country were composed of small communities like Burlington, connected to the grid by telecommunications, then we probably wouldn’t have an epidemic problem at all.

Most people already know what we should be doing right now using what is currently possible. But Katrina reminded us that if we make a plan, we must make sure that we can actually use it in a timely manner. The best plan in the world is useless if it isn’t implemented in time. The political will of individual leaders must be assured, and the culture of bureaucratic obstacles must be circumvented.

In the next 10 to 20 years, we can invest in more flexible technologies like the aforementioned viral competitors. When we discover what molecular components are consistently required by all influenza viruses, then we can develop more universal DNA vaccines that will protect against all influenza viruses and be less affected by mutation. Most of the telemedicine technologies that we discuss in greater detail in other papers already exist, but it will take a few years to implement them. And, whether or not we want to actually use the military itself is a question, for it has a number of useful technologies and lessons that could be applied to the disaster community. The Incident Command System is an adaptation of a military model. An important lesson to learn from the military is that, if they arrive in an area without infrastructure, they build their own. They build airports, provide electricity, and construct bases. The disaster community should make fewer assumptions about local resources, be prepared to provide their own, and definitely be self-sustaining for longer than 72 hours.

Farther in the future, the military’s Future Combat System (FCS) envisions a battlefield medical system that includes portable, individual intensive care units called Trauma Pods. An array of manned and unmanned vehicles connected to a network will transport patients and ultimately provide medical interventions as well. Such a system would take the human vectors out of the loop, maintain the integrity of quarantine, and prevent the spread of disease without sacrificing care. The command and control apparatus must be isolated—before an event—in order to ensure command throughout the event. Aegis cruisers connected to the network could provide an ideal medium for such isolation, but it must happen now. Again, most measures instituted after we have identified that an event is underway are too late.
Ultimately, the healthcare system upon which any biological disaster response is based needs to be transformed. Healthcare and medical services is listed as Emergency Support (ESF) number eight of 12 in the NDMS. Other ESFs include transportation, communication, energy, and the like, but number eight is unique. Healthcare requires every other ESF in order to operate, and every other ESF relies on healthcare. New Orleans cannot be repopulated without a healthcare system in place, but everything else must be in place first. So healthcare must take a more central role in disaster planning. When we were once asked to uncover vulnerabilities in the US healthcare system—to figure out how a terrorist could break it—we immediately realized two things: 1) it’s not a system, and 2) it’s already broken. How can the same system that operates well below capacity and can barely provide healthcare to all of its citizens on a daily basis be expected to suddenly respond to a disaster? Figure 2 depicts the trends that need to happen in healthcare in order for it to be more capable of handling a pandemic.

First, private healthcare, public healthcare, and national security need to be combined into a single entity because any one of them is ineffective without the other two. Second, healthcare capabilities should be more evenly distributed throughout the system using telecommunications and teledicine. Along these same lines, the majority of healthcare delivery should be moved out of the hospital and into the community and the home.

Federal resources can’t be in a million places at once. FEMA isn’t going to respond effectively to 100 outbreaks of avian flu scattered across the country. The near future requires a rethinking of the way our system is designed. Imagine the human immune system. A newborn’s immune system never receives a list of the numerous pathogens it will encounter in the course of a lifetime, but it adapts. There is no central command, but it remains exquisitely regulated. It is an organic, evolving network whose intelligence is derived from rules and interactions rather than the agents themselves. The details—the unpredictable part—are less critical. The system begins

Figure 2. The healthcare system needs to evolve in order to respond to pandemics.
before the event and evolves as the disaster unfolds. A variety of approaches function simultaneously, and successful ones are reinforced on a fitness landscape. Simple components interact to create emergent behavior much more complex and flexible than a system controlled by a single entity. Foreknowledge is unnecessary; synchrony is built in. Emerging threats are autonomous and self-replicating. Our response system ultimately needs to look more like this to be truly effective.

A paradigm shift is in progress. The old paradigm is to try to conform the disaster to the response: to control. The new paradigm is to conform the response to the disaster: to adapt. The goal is simple: to create a system based on a realistic set of assumptions in order to prevent tactical events from assuming strategic proportions. While it may not be possible to prevent future attacks entirely, it is possible to ameliorate, contain, and mitigate their social and political effects. Doing so is crucial to the preservation of national capabilities and political will and, with them, US leadership both domestically and abroad.

Biological threats are potentially so devastating, in part, because our healthcare system in its current state is itself a strategic vulnerability. Therefore, revolutionizing our response capabilities would necessarily involve improving our delivery of healthcare. Investing large amounts of time and money retrofitting a system that we hope to never use may be politically unpalatable, even if it would serve as a deterrent to attack, since our current system practically invites it. However, reorganizing the dual-use system of healthcare would not only benefit our citizens on a daily basis but also protect the United States from natural pandemics and even biological terrorism.

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REFERENCES

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