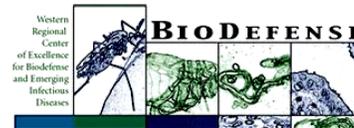


# Responding to Influenza Pandemics

**Findings from the Task Force on  
One-Health Approach to Influenza  
*Assessment of Critical Issues and Options***  
December 1-2, 2009  
Washington, DC



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## **Responding to Influenza Pandemics**

**Prepared by Neville Clarke, Terry Nipp, Tom Powdrill, and Jennifer Rinderknecht**

The DHS National Center for Foreign Animal and Zoonotic Disease Defense and the NIH Western Regional Center of Excellence for Biodefense and Emerging Infectious Diseases served as the conveners of a Task Force of some of the nation's leading influenza experts to examine how influenza pandemics emerge and future research needs. The Task Force convened at a workshop held in Washington, DC on December 1-2, 2009.

The Task Force was asked to utilize the current H1N1 pandemic as a case study, and to consider how a better comprehension and application of our knowledge about the "animal-human-environment interface" will enable us to better understand why some pathogens are a cause of a simple influenza season, whereas others lead to global outbreaks with potentially deadly disease and/or overwhelming impacts on public health and medical capacity. Building on a better information of how diseases move from one type of host to another and the role of environmental factors, the Task Force was asked to identify possible new strategies and technologies that can be developed to prevent and better manage future pandemics. The Task Force was asked to consider how applying the principles of the "One Health" (also known as "One Medicine", "One World", and other terms) approach could contribute to the detection and management of zoonotic pandemic events.

The Task Force includes experts from diverse fields and disciplines, including: the molecular biology of influenza viruses, immunology, virology, public health, veterinary and human medicine, wildlife ecology, and epidemiology. A summary of the workshop discussions and the findings of the Influenza Task Force follow<sup>1</sup>:

### **1. A real and present danger**

At the time of the Influenza Task Force Workshop, the Centers for Disease Control and Prevention (CDC) estimated that in the United States alone the A/2009 (H1N1) pandemic influenza A virus had:

- Infected between 43 million and 88 million people;
- Hospitalized between 192,000 and 398,000 people; and

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<sup>1</sup> The consensus findings of the Task Force do not necessarily represent the opinions or positions of any individual participant on the Task Force or that of their organizations. For more information about the Task Force and the Workshop Proceedings, please visit: <http://fazd.tamu.edu/>

- Killed between 8,720 and 18,050 people<sup>2</sup>.

While these numbers are deadly serious, it could have been, and still could be, far worse. During the infamous Spanish influenza pandemic, the A/1918 (H1N1) virus killed an estimated 50-100 million people worldwide (more than the total number of deaths in both World Wars combined or double that of total military deaths for both wars). In the United States alone, 28% of the population was infected and an estimated 675,000 Americans died.

Every year there are new outbreaks of influenza. What causes certain strains of the influenza virus to become more transmissible and produce more serious infections? On examination of the A/2009 H1N1 pandemic, it becomes clear that many, if not all, elements for a potential pandemic exist every year. When considering this and the viruses involved, the real question may not be “why are there pandemics,” but rather, “why don’t we have influenza pandemics more often than history has documented?” Since there is a very real potential for an influenza pandemic in any given year and modern transportation ensures that influenza viruses can be spread almost worldwide within 48 hours, it becomes urgent to consider what science can inform us about why we do not have more frequent pandemics. When a pandemic does occur, science can determine the signature factors at the environmental-animal-human interfaces associated with the emergence and spread of the virus. We can then consider what the most efficacious and cost-effective steps are to manage and even prevent future pandemics.

As we consider the development of science-based preventive medicine management strategies, it becomes apparent that preventing pandemics is much like preventing acts of terrorism – to be 100% effective the programs and strategies that are put in place have to work every time; a tough requirement, while the elements that lead to the development and spread of a pandemic

disease or terrorist attack only have to collectively work once to succeed. Mother Nature and terrorists are very similar in that they can be very patient, thus requiring a high level of commitment and vigilance to prevent future pandemics and terrorist attacks. However, in the case of an influenza pandemic, it is not hundreds or even thousands of people that may be at risk, but literally tens of millions of people could die if we fail to invest time and resources to determine what can be done to most effectively control (or ideally prevent) the next influenza pandemic.

### **One Health**

*The One Health concept is not new – its roots in comparative medicine and pathology extend beyond the last century (Virchow, Osler). The idea has been extended by visionaries such as Calvin Schwabe and Joshua Lederburg in the latter part of the twentieth century. There is growing recognition and support for developing a One Health approach to anticipating and managing potentially catastrophic biothreats, such as pandemics. The challenge is not so much in reaching agreement on the One Health idea, but rather in building the conceptual frameworks and collaborative relations that can make it possible to truly implement the approach.*

## **2. The One-Health Approach and Influenza**

The recent emergence of the A/2009 (H1N1) influenza virus in humans and its escalation into a pandemic threat are examples of how established and potential

<sup>2</sup> CDC Estimates from April 2009– March 13, 2010, [http://www.cdc.gov/h1n1flu/estimates\\_2009\\_h1n1.htm](http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm)

zoonotic agents can circulate undetected in animal populations and subsequently enter the human population by heretofore relatively unpredictable mechanisms. In order to detect and respond in a timely manner to zoonotic diseases that can impact humans, it is clear that we need to monitor the spread of zoonotic disease agents as they emerge and circulate among other animal species. The “One-Health” approach recognizes that infectious agents may cross into multiple species and cause disease. Of all the infectious agents known to infect humans, 60% of them are classified as zoonotic. This necessitates developing a broader and more comprehensive approach to understanding and responding to infectious agents in birds and lower mammals, as well as the interactions that exist at avian-lower mammal-human interfaces. Very simply put, since some diseases can be transmitted between birds/animals and humans, a “One Health” approach that integrates animal and public health along with relevant environmental factors provides critical new approaches and tools in combating infectious disease health threats to humans and our food supply.

For example, to establish the interaction of multiple species in the genesis of the A/2009 (H1N1) pandemic influenza virus, one need look no further than the ancestral origin of the eight RNA segments that make up the genetic composition of this pandemic virus. Two segments are North American avian-like (PA, PB2), 1 is human-like (PB1), 3 are North American swine-like (HA, NP, NS), and 2 are Eurasian swine-like (ultimately avian, NA, M). From a broader standpoint, besides the H1, H2 and H3 hemagglutinin subtypes that are known to infect people, wild birds, especially aquatic waterfowl, carry a vast repertoire of influenza genes including that for all of the 16 potential hemagglutinin (HA) and 9 neuraminidase (NA) subtypes of type A influenza viruses. Current evidence regarding all influenza pandemics of the 20<sup>th</sup> Century, including those caused by the Spanish 1918 (H1N1), Asian 1957 (H2N2), and Hong Kong 1968 (H3N2) viruses, suggest the genomic origination from the avian pool either through reassortment of viral segments in intermediate hosts coinfecting with more than one type of virus, or direct transfer (Ref. Salomon and Webster, Cell, 2009). Layered upon this complexity of genomic reassortment and multiple potential intermediate hosts (including humans and animals) is the fact that viral RNA polymerases are notoriously error-prone during RNA replication resulting in a nucleotide mutation rate of up to a million times greater than that of vertebrate DNA polymerases. Thus influenza viruses, including the current A/2009 (H1N1) pandemic virus, readily acquire mutations at a rapid rate leading to further diversity and providing them the ability, through population dynamics, to quickly accommodate and circumvent environmental challenges including host receptor specificity, herd immunity, replication efficiency, and vaccine and antiviral drug selection pressures.

The “One-Health” approach recognizes that the distinctions between “animal health and human health” are not always meaningful and that many times we must address both human and animal health at the same time in order to address either successfully. The importance of addressing animal and public health as part of an integrated whole has been recently emphasized by a Summit Conference of the One Health Commission in November, 2009, in conjunction with the National Academies. The *One Health Commission* Summit set the stage for the work of the *One Health Commission*, which was created to establish closer professional collaborations and educational opportunities across the health science professions and their

related disciplines. At the outset of the meeting, an announcement was made by Clyde Behney, Deputy Executive Officer of the *Institute of Medicine*, who shared that the intent of the Institute of Medicine and National Research Council to conduct a study that will help shape the *One Health* vision at the national and international level. The results of their study will be utilized to develop a strategic roadmap for public and private policies and initiatives that will be instrumental in shaping the implementation of the *One Health* vision. Where the Commission and the Academy are further developing the broader principles and visibility of the One-Health approach, this Task Force Workshop was developed to look at the application of these principles in practice using the H1N1 pandemic as a case study of the interdependence of human and animal hosts in the genesis of the current circulating H1N1 virus.

### **3. Discussion Topics**

The participants of the Influenza Task Force Workshop were asked to focus their discussion within four thematic topics, in order to identify researchable knowledge gaps.

- Epidemiology and Surveillance
- Transmission Dynamics
- Immunobiology and Vaccines
- Molecular Approaches and Pathobiology

It was recognized that these topics are interrelated, and often key points made in one thematic discussion shed light on the issues and challenges in another. In the following section, the discussions of the workshop are summarized within the four thematic topics; the Findings of the Task Force are listed within each thematic area. Appropriately, during the discussions several key concepts emerged that cut-across these four themes and these are summarized in the following section. The Task Force discussions focused on researchable gaps and observations related to the zoonotic potential of influenza viruses in general, and H1N1 specifically, that can be best addressed through the application of an integrated “One Health” approach.

#### **3A. Epidemiology and Surveillance**

One of the most important and intriguing issues related to epidemiology and surveillance is the involvement of multiple animal hosts in the genesis of the current strain. As has been noted, no animal to human transmission of the current A/2009 (H1N1) pandemic virus been documented as yet, though there are clear indications that there have been transmissions from humans to animals. When and where the multiple reassortments and nucleotide changes among avian, porcine, and human influenza genomic segments occurred to generate the pandemic strain may be possible to infer retrospectively. However, the very limited and fragmented surveillance in animal species was not sufficient to provide any predictive capability to foreshadow the outbreak. Furthermore, it is not immediately clear what the host range specificity of the current virus is – since the beginning of the outbreak cases of human to swine transmission, infected turkey flocks and companion animal infections including felines, ferrets, and possibly canines have been documented. Of course, a prime concern here is that further reassortment, including

but not limited to reassortment with the H5N1 strain, may occur to generate a virus of higher consequence for either humans or animals. Layered on this complexity are the facts that a very large number of avian species are capable of harboring most if not all influenza subtypes and many of these species are migratory.

The structure of the agricultural world also poses unique challenges for systematic and relevant surveillance for influenza virus and other emerging pathogens. Large commercial operations, such as in the poultry and swine industries, often have internal surveillance and biosecurity measures to safeguard their investments. However, there is little incentive to submit samples for general veterinary or public health analysis, and in some cases, the viruses submitted to commercial companies for autologous (“custom-made”) vaccine development are the intellectual property of the owners and do not contribute to the public influenza virus sequence databases. There are large private databases of influenza viruses in multiple states (and countries) that are confidential and currently inaccessible to public bioinformatic analysis, thereby leaving significant gaps in our knowledge of circulating virus strains. Furthermore USDA-APHIS does not have a mandatory reporting and monitoring requirement for influenza in swine operations, so surveillance participation by operators is strictly voluntary.

On the other end of the spectrum from large commercial operations are the smaller, often family-owned and non-commercial premises, where public health concerns related to surveillance may be minimal to non-existent. These premises also may promote intimate contact and mixing of several species, such as swine, poultry, humans, and wildlife, thereby facilitating virus transfer between multiple species. Similarly, cultural practices such as live bird or “wet” markets where multiple species of birds, animals, and humans co-mingle also represent a potential hot spot of new virus emergence and a significant gap in surveillance activity. Finally, the growing interface between wildlife and domestic animal populations is extremely difficult to monitor –areas of concern include the large feral swine population, with potential for encroachment upon domestic animal and human populations, and migratory birds, which can disperse disease agents over long distances.

#### ***FINDINGS: Expand and improve surveillance***

Because of insufficient influenza virus surveillance data, it was not possible to anticipate the emergence of the H1N1 strain, and it remains a challenge to understand fully how it developed. Improved surveillance could make it possible to detect and respond to a potential pandemic early enough to greatly reduce its impacts. Possible steps to improve influenza surveillance were identified by the Task Force.

- Establish programs of sustained, broad human and animal surveillance to monitor for influenza virus in healthy sentinel species in priority locations. This will make it possible to accurately populate genetic and epidemiology databases and to provide for the development of appropriate diagnostic reagents and representative strains for vaccine development. Surveillance should focus on:

- People who work closely with animals on a sustained basis, such as people who work directly in the poultry and swine industries;
  - Domestic animals of concern, such as swine and poultry, and additional potential hosts, such as horses, dogs and cats;
  - Targeted wild and feral animals, such as feral pigs and wild aquatic birds.
- Certainly, such targeted surveillance must be carefully considered before implementation. Among many concerns to be addressed to answer “How would this be done?”
  - How many sites would be used for testing?
  - What is the necessary scale for obtaining good information?
  - How much would it cost? (Cost: benefit analysis)
  - What entities would be responsible for implementation?
- Methodologies for surveying for animal and wildlife influenza virus infection should be evaluated to develop the most efficient surveillance techniques and assays and to optimize strategies for sampling and monitoring target influenza virus host populations.
- In addition to enhanced surveillance within the U.S., a new level of global surveillance needs to be developed. In concurrence with several other groups, the Task Force agreed that an influenza A virus surveillance program of domestic poultry and swine and related workers should be established in potential hot spots such as southeastern and eastern Asia and possibly Africa.
- Where there may be sensitivity to collecting surveillance data, enhanced surveillance may be accomplished by use of non-invasive measures, such as air sampling, water sampling, oral fluid sampling, and litter sampling. Proof-of-concept would first need to be established in pilot projects to establish feasibility of this approach. In addition, policies for management of surveillance data could be developed and implemented that preserve anonymity and obscure site-specific locations. Efforts should be made to communicate with the agricultural animal industries to develop acceptable mechanisms by which the essential components of the human and animal health communities can have appropriate access to privately held information about the spread of influenza viruses.
- In principle, the Task Force endorses the recommendations made by the Institute of Medicine /National Research Council in its report, “Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases”. ([http://www.nap.edu/catalog.php?record\\_id=12625](http://www.nap.edu/catalog.php?record_id=12625)).

### **FINDINGS: *Improve early detection***

In tandem with assuring that there are comprehensive surveillance programs in place, these programs need the latest in new tools for early, accurate and sensitive detection and identification of the influenza viruses.

- Priority should be given to applying developments in molecular biology and genomics to increasing diagnostic and detection capabilities, including the possible use of hand-held field devices.
- Bioinformatics and visual analytics should be applied to aggregating and analyzing the masses of accumulating data and for finding critical intervention points in the patterns of interrelations that can emerge from the data.

### **3B. Transmission Dynamics**

Understanding, measuring, and controlling transmission is more difficult than other parts of the problem, and is heavily dependent on effective surveillance and analysis. One of the most important principles regarding the transmission of influenza viruses is the fact that infectivity of certain hosts does not result in apparent clinical morbidity (In other words, an asymptomatic carrier). In addition, the traditional view of sialic acid receptor preferences dictating host specificity is incomplete and no longer sufficient to explain viral tropisms and species specificity or the lack thereof. A more complete analysis of all genomic segments is necessary to determine effective markers for cross-species transmission. The triple reassortant internal gene (TRIG) cassette of the current virus is still not well understood in relation to the potential for human and animal infections. At least 10 different genotypes of virus have been circulating in swine since 1998, and it is unclear how many may have caused human infections.

Limiting transmission also poses unique challenges. There are obviously optimal thresholds for contact among humans and animals to promote cross-species transmission. A case in point is swine workers, of whom there are approximately 300,000 in the U.S. There are models which suggest that swine workers should be vaccinated as a first line of defense for the prevention of human outbreaks. However, as with the case for animals, it is not clear whether vaccination provides an effective barrier against virus transfer, although it may alleviate clinical disease in the vaccinated host. In any case, swine workers and others intimately involved with activities at animal human interfaces represent an excellent sentinel population for surveillance for cross-species transmission. It is also important to realize that the transportation of swine and other animals involved in commercial agriculture is an additional means of virus dissemination to other animals and potentially human hosts.

Finally, it must be recognized that influenza viruses represent a constantly evolving genetic pool of material existing in multiple species. Given the virus's capability of mutation and reassortment, the number of potential influenza virus strains functionally approaches infinity and begs the question of why there is not a pandemic every year. As stated above, the current

H1N1 strain is known to infect pigs, turkeys, cats, dogs, and ferrets. As some or all of these species harbor other influenza viruses, the possibility for the emergence of new reassortants and novel virus strains must be seriously considered. The involvement of companion animals is a particular concern, as these animals have not historically been widely considered as hosts for influenza viruses, yet this population lives in daily contact with humans. As such, domestic pets may also be regarded as a priority for strategic surveillance.

**FINDINGS: *Develop new tools to interrupt transmission***

We do not have sufficient genetic information about influenza viruses to develop the signature markers that define species specificity and therefore, little ability to track the movement of viruses across species. If we improved our ability to identify and track the viruses as they evolve, we would be better positioned to recognize critical intervention points and thereby interrupt transmission of the disease, particularly between animals and humans.

- High priority should be given to complete sequencing and fine mapping of all of the genomic segments of critical influenza virus isolates, not just the HA, NA and M segments.
- There should be increased collection and timely sharing of influenza viruses and sequences from wild/domestic animals, so as to provide an open-source database for evaluation of novel strains and mutations of concern.
- As mentioned previously, increased surveillance at the human-animal interface should lead to strategic interventions in populations that might otherwise transmit and spread the virus.

**3C. Immunobiology and Vaccines**

One of the most glaring gaps in our preparedness for the H1N1 outbreak was the inability to translate virus detection and characterization into effective vaccines in an efficient and timely manner, and many of the same issues that limited pandemic H1N1 vaccine development similarly limit seasonal human and animal influenza vaccines. The most effective tool for influenza prevention in humans is vaccination, so under this premise it is imperative to improve both vaccine technology and domestic production capabilities. Advances are already occurring in other countries, and there are current developments within the U.S. to do so. In addition, investigation of the use of adjuvants as a means for both immune stimulation and dose sparing effects has not been as actively developed in the U.S., although also adopted and approved in other countries and employed in animal vaccine formulations.

Optimal vaccine development requires enhanced information sharing and collaboration between human and animal health officials. One specific obstacle, as mentioned previously, relates to autologous vaccine production for swine producers. These vaccines may be produced in a manner of weeks and must meet safety and purity standards, but do not require efficacy

testing. The sequences of these viruses are privately held, and thus do not contribute to our knowledge and understanding of circulating virus strains. In addition, there is minimal to non-existent understanding of swine virus isolates from the developing world. And a final obstacle to vaccine improvement is an undercurrent of anti-vaccine sentiment for human vaccination and fear based upon non-scientific risk perceptions.

Collaboration between the two regulatory agencies involved in vaccine licensure (FDA and USDA) represents significant opportunities for streamlined vaccine development and the adoption of new vaccine technologies. In order to expedite this process, it is necessary to understand more about the correlates of protection, including cell mediated immunity (CMI) as well as the role of heterologous immunity to different vaccine strains. In swine vaccine usage, strain mismatch in the field has actually been associated with more severe lung lesions upon challenge infection. Lesion scores were elevated from 5% to 25% in mismatched immunized animals. Interestingly, this effect has only been noted for killed vaccines and not modified live virus vaccines. Also not well understood is why some HAs are more immunogenic than others and what methods may be employed to improve HA presentation to the immune system. An ultimate goal may be the development of a universal vaccine that could provide protection across viruses of all 16 HA subtypes and could be used in both humans and animals. Short of this, it may be possible to increase the valency of vaccines to provide as broad coverage as possible.

#### ***FINDINGS: Improve vaccines and vaccine production***

The faster we can move vaccines into production, the more likely we will be able to disrupt transmission through the vaccination of target groups at the human-animal interface. Highly transmissible emerging infectious diseases can spread almost exponentially during their early phases. Reducing the time it takes to produce a new vaccine from months to weeks could save tens of thousands of lives.

- There is an immediate need for more affordable, more effective, and easily deliverable vaccines that are more rapidly approved, distributed, and administered.
- Current efforts to transition from egg-based vaccine to cell culture vaccine production should be supported and facilitated.
- Emphasis should be placed on improving human and animal influenza vaccines by –
  - Using new vaccine technologies/platforms and adjuvants
  - Optimally utilizing adjuvants (dose sparing/enhancing immunity)
  - Expanding domestic and global human influenza vaccine production
  - Streamlining the regulatory process for both animal and human influenza vaccines
  - Recognizing that the necessary strain change for animal vaccines is faster than we have historically been prepared to accommodate.

- Autologous vaccines may play a critical “short-gap” role in meeting the need for immediate vaccines, but their effectiveness should be evaluated, as should their role in driving evolution of influenza viruses.
- Enhanced interactions should be supported between veterinary medical authorities (OIE, FAO) and the WHO Global Influenza Surveillance Network during vaccine strain selection meetings.

### **3D. Molecular Approaches and Pathobiology**

An overarching question is to what degree modern and future biological and associated informatics technologies may contribute to our abilities to predict, prepare for, prevent, and mitigate the consequences of future high-consequence influenza or other zoonotic disease emergence. The current pandemic has been referred to as an “infodemic” because of the rapid dissemination of information, including viral sequence availability to the scientific community at large. Current sequencing technologies allow deep sequencing of virus isolates, revealing the abundance of quasi-species, as well as elucidating the presence of mutations arising by propagation of virus in egg or cell-based systems. Other tools, such as bead-based array systems, high throughput nucleic acid and antibody analysis robotic systems, and microarrays are creating mounds of data for bioinformatic analyses. Perhaps one of the most critical applications of these technologies is the investigation of host-pathogen interaction and response.

The current H1N1 strain illustrates the wide variety of clinical manifestations in humans ranging from ordinary seasonal flu symptoms to fatal, acute viral pneumonia. In addition, the contribution of risk factors for fatal infection, including pregnancy, obesity, and age, is not fully understood. Autopsy investigations of approximately 100 fatal human cases has shown potentially important differences between fatal H1N1 and ordinary seasonal infections with regard to the involvement of upper and lower respiratory tracts and the viral load indicated by immunohistochemical analysis. Although approximately 30%-40% of the fatal pneumonias were complicated by bacterial super-infection, the fact remains that the larger percentage were primarily viral pneumonias. Elucidation of the mechanisms of the predisposing factors leading to serious or fatal cases is needed in order to stratify patient populations and identify those individuals for targeted intervention strategies.

The further development of appropriate animal models for human infection, including ferrets, guinea pigs, and non-human primates is an important part of the equation. Detailed genomic and transcriptomic analyses tracking both host and pathogen response *in vivo* have the potential to unlock unknown pathways exploited by the virus to identify targets for therapeutic development.

***FINDINGS: Apply new developments from the fields of molecular biology***

In all areas of response to influenza, from detection and surveillance to tracking the spread of a new virus strain to the development of more effective vaccines, it is critical to understand the underlying mechanisms at the molecular level. Emerging developments in “-omics” tools including but not limited to those for genomics, transcriptomics, proteomics, epigenetics and associated bioinformatics for both host and pathogen hold forth promise of providing understanding at the most fundamental levels of how a lethal virus evolves and how its transmission and spread might be stopped. As one example, the development of reverse genetics for the creation of experimentally designed influenza viruses allows researchers to investigate the phenotypic manifestation of viral genetic determinants in several animal hosts and shows the promise for accelerated vaccine development.

- Based on our emerging understanding of genomics, a new nomenclature system for influenza viruses should be developed to prevent confusion about the nature and source of viruses in the public mind. In this regard, definition of the 2009 pandemic H1N1 virus as “swine flu” has had significant economic and psychological impacts on the swine industries of North American and beyond.
- Host factors such as genetic resistance, genetic variability of immune response, and risks for severity need to be better defined.
- Greater information is needed regarding influenza epidemiology, genetics, genomics, and transcriptomics. That data must be organized to facilitate rapid exchange of information at the global level to speed the response to emergent strains, from both animal and human sources.
- The gap needs to be closed between knowledge of influenza RNA sequences and consequent changes in viral protein antigenicity or function (e.g., rate of replication, ultimate titer achieved, and level of avoidance of host defenses).

#### **4. Cross-Cutting Challenges**

##### ***Harness the One-Health Approach***

Within each of the four discussion topics, it is clear that the One-Health multi-disciplinary and multi-institutional approach of integrating public human and animal health is essential for future successes in preventing and controlling influenza pandemics. Coordination and communication across existing organizational structures and domains of expertise are essential. Regarding epidemiology and surveillance, it is necessary to not only implement but also coordinate detection and monitoring across multiple species, rather than waiting until a novel pathogen has already impacted humans. From the perspective of immunobiology, this early detection and characterization of the emerging virus in other species is necessary to expedite development of human vaccines. This achievement will require the development of data systems that make pathogen and host information available from diverse sources in agriculture, wildlife biology, and human health. The process of developing vaccines can be improved by

harmonizing animal and human vaccine methodologies. From molecular approaches, better knowledge of genomics and transcriptomics of the pathogen and diverse hosts is needed in order to better understand the genesis and pathogenesis of the viruses and to develop new approaches to interrupt their transmission. And from transmission dynamics, the best way to prevent a pandemic of human influenza may be to prevent development of novel viruses in other species and to interrupt the transmission of such viruses between animal and human hosts.

The recent experiences with H1N1 have reinforced our understanding that zoonotic diseases must be addressed with in a comprehensive and integrated fashion. The influenza virus can transform and evolve as it interacts with and spreads across diverse hosts. Our responses must accordingly transcend specific host species, and we must use a full range of disciplines as we seek to interrupt the transmission of the disease in the complex web of host-pathogen interactions in the environment. Even earlier detection and vaccine development could be facilitated through the establishment of standing detection and surveillance programs that more fully harness the expertise of diverse disciplines and agencies in the fields of both public human and animal health.

#### ***Foster multi-agency collaboration***

In order to successfully respond to and prevent future influenza pandemics by utilizing the One-Health approach of integrating animal and public health efforts, federal and state government agencies must rise to a new level of sustained collaboration. Continuous close cooperation is essential between the Department of Agriculture (USDA) and the Department of Health and Human Services (HHS), especially involving the National Institutes of Health (NIH), and the Centers for Disease Control (CDC), along with the Department of the Interior (DOI). Collaboration among these and other federal agencies has to be mirrored and integrated with parallel efforts by state governmental agencies. While this is an essential and obvious recommendation to make, territorial challenges may make it a very difficult goal to actually implement. Each federal and state government agency already has a full portfolio of missions and mandates. The authorizations and funding mechanisms for each agency do not lend themselves readily to the collaboration that will be necessary. As with other challenges that require multi-agency collaboration, support and guidance from the Administration will be needed to provide the necessary level of priority and focus to successfully prepare to prevent future influenza pandemics.

#### ***Support new approaches to research and data collection***

The Task Force spent considerable time discussing how to address the knowledge gaps and research needs identified during the workshop. Of course, there is a real need for new investments in research and data collection to address these knowledge gaps. New funding is required within each of the involved agencies to support the research and data collection needs discussed previously in this report. But in addition to needing significant new investments, the Task Force recognized that a new approach to funding this type of research and data collection

will be critical. Existing research programs in USDA, NIH, NSF and other agencies were designed to address the primary missions of their respective agencies. Appropriate mechanisms have been developed to avoid duplication between the science funding agencies and to avoid “mission creep”. Traditionally, USDA has focused on research that addressed agricultural animals. NIH address research that is focused on human health consequences, and NSF has focused on basic biology at the molecular level. However, addressing knowledge gaps and research needs in the area of zoonotic diseases requires transcending these distinctions and taking a comprehensive and integrated approach to understanding the interactions between diverse host species and pathogens as they interact in the environment, both at the organism and molecular level. Existing funding mechanisms and administrative structures may need to be modified and new opportunities may need to be developed that will foster an integrated and comprehensive approach to zoonotic diseases under the One-Health concept.

### ***Preparing for the unpredictable***

To predict when and where the next influenza pandemic will emerge, it will be necessary to know things we simply do not currently know. Knowledge gaps will need to be addressed in order to develop better models for predicting the emergence of pandemics. But while improved science-based knowledge will assist in the control of future influenza pandemics, the ability to use this knowledge to predict when, where and how a pandemic may emerge will likely remain elusive. Each year brings a new “roll of the genetic dice” for different combinations of host-pathogen interactions so that predicting which new virus may lead to a pandemic, and when it will, will likely remain problematic.

However, while we cannot predict, we can certainly prepare. With preparation, we can detect the earliest signs that a new strain of the virus is emerging so that we can initiate strategies that are ready to go. With preparation, we can have new vaccines in production within weeks, not months. With preparation, we can activate the public human and animal health communities to recognize and respond appropriately to the latest threat. With preparation, we can target and successfully immunize critical populations to minimize the spread of the disease. But in order to prepare, efforts must begin now to address the knowledge gaps identified in these Task Force discussions and to foster the level of interagency collaboration that will be needed.

### **The Challenge at Hand**

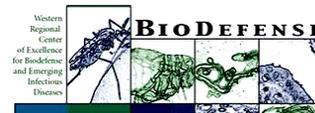
Just as previous Administrations and Congresses have collaborated to develop new, more integrated approaches to other challenges, such as global climate change or meeting our nation’s energy needs or responding to terrorism, preventing global influenza pandemics will require the same kind of attention from our nation’s leaders. As with these other initiatives, we must move sooner, not later. In some fashion, the current H1N1 pandemic provided a “test case.” We have had the opportunity to see what works and what will need to be done better in the future. We have the opportunity to learn from this experience and strive to prevent the next pandemic, which could be far more catastrophic than H1N1 has been thus far.

There are many calls to action, and it is easy to become indifferent to the need for yet another initiative, but the threat of another influenza pandemic is real, imminent, and indeed permanent. We can use the lessons provided from the H1N1 pandemic, or not. We can prepare now to help prevent the next pandemic, or not. Millions of lives may hang in the balance.



**Task Force**  
**A One-Health Approach to Influenza**  
***Assessment of Critical Issues and Options***

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11/29/09

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Korch, George	Senior Science Advisor, Office of the Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS), (Former Commander, United States Army Medical Research Institute for Infectious Diseases)
Ksiazek, Tom	Galveston National Lab, University of Texas Medical Branch (UTMB) at Galveston (Former Chief, Special Pathogens Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention (CDC)
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Murphy, Fred	Dept. of Pathology, University of Texas Medical Branch (UTMB); Galveston National Lab; Institute for Human Infections and Immunity, NIAID Center for Biodefense and Emerging Infectious Disease
Nipp, Terry	Assistant Director, Special Projects, National Center for Foreign Animal and Zoonotic Disease Defense (FAZD Center)
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Parker, Gerald	Principal Deputy Assistant Secretary, Office of the Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS)
Powdrill, Thomas	Assistant Director for External Affairs, National Center for Foreign Animal and Zoonotic Disease Defense (FAZD Center)
Pappaioanou, Marguerite	Executive Director, American Association of Veterinary Medical Colleges (AAVMC)
Perez, Daniel	University of Maryland, Principal Investigator, NIH Center for Research on Influenza Pathogenesis
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Snowder, Gary	Associate Director, National Center for Foreign Animal and Zoonotic Disease Defense (FAZD Center)
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Zaki, Sherif	Chief of Infectious Disease Pathology, Centers for Disease Control and Prevention (CDC)

**Task Force on One-Health Approach to Influenza -  
*Assessment of Critical Issues and Options***

December 1-2, 2009  
Hall of States – Room 231  
444 North Capitol St NW, Washington, DC

**Agenda**

**December 1, 2009**

**8:30**           **Welcome** – Neville Clarke and David Walker  
Facilitator – Terry Nipp

**8:35**           **Purpose of Meeting – Goals and Objectives** – Fred Murphy and  
George Korch

**8:45**           **Self Introductions** – Task Force Members briefly introduce themselves –  
name, affiliation, major specialty

**9:05**           **Approach to Meeting** – Neville Clarke

The first day's agenda has been divided into four session topics, realizing that the topics may have substantial overlap. These topics are:

1. Epidemiology and surveillance
2. Transmission dynamics
3. Immunobiology and vaccines
4. Pathobiology and application of modern molecular technologies

The discussion ensuing will be open-ended; however, some relevant questions to be addressed have been suggested for each topic. Some issues will emerge that are cross-cutting and will likely need to be considered in different sessions, such as the possible need for alternatives to current animal models.

**9:15**           **Epidemiology and Surveillance**

**Introduction-** Richard Slemons and Mark Miller

Potential/example questions to be addressed:

1. If extensive surveillance and monitoring in multiple species, including wildlife, is the key, is this possible, particularly on a global scale?
2. Given the exponential development of rapid and portable molecular diagnostic devices, will we one day be able to provide usable and predictive data to epidemiologists and decision makers in near real time?
3. Given the global nature of the surveillance problem, will other countries cooperate? When surveillance data is not likely going to be available, what are possible ways to work around the chronically unavailable data?

**10:45 Coffee and Informal Discussion**

**11:15 Transmission Dynamics**

**Introduction-** Chris Olsen and Daniel Perez

Potential/example questions to be addressed:

1. Can we find better predictors for the emergence of potentially pandemic or highly pathogenic influenza strains in multiple species?
2. Now that the virus has now been identified in turkeys, commercial swine herds, ferrets, and domestic cats, are there additional concerns relating to new reassortant strains of high consequence to human or animal populations?

**12:45 Lunch**

**1:30 Immunobiology and Vaccines**

**Introduction-** Marcus Kehrill and Nancy Cox

Potential/example questions to be addressed:

1. Can we develop effective vaccines faster with broader coverage using advanced vaccine technologies?
2. Can we make intelligent decisions about when to vaccinate, particularly in animal species where vaccination may select for escape mutants?
3. Is it possible to successfully vaccinate domestic and/or wildlife species sufficiently to protect human populations?

**3:00 Coffee and Informal Discussion**

**3:30 Molecular Approaches and Pathobiology**

**Introductions-** Sherif Zaki and Rick Pyles

Potential/example questions to be addressed:

1. What role can modern genomics play in the prediction and/or prevention of the next pandemic?
2. Will study of the basic host-pathogen biology of the virus in multiple species lead to new insights for the development of new antiviral strategies – is there an Achilles heel? Given the flexibility of the virus, will it find a way around these also?
3. Are there any predictors for increased virulence in the current H1N1 strain?
4. What aspects of modern technology may be implemented in resource-limited settings?

**5:00 Wrap up and Plans for Day 2**

**5:30 Recess**

**6:00**            **Group Dinner**  
**Dr. Gerry Parker – HHS-ASPR – Comments on Status of the H1N1**  
**Pandemic and Lessons Being Learned**

**December 2, 2009**

**8:00**            **Discussion and Summary of Findings and Conclusions from First Day**  
**Discussions – Neville Clarke**  
The discussions of the second day have been left unstructured; to make sure that there is full opportunity to cover topics that emerge that do not necessarily fit within the sessions of the first day and to consider new issues that emerge. Given the participants at the workshop, we are confident that there will be a full range on interesting ideas that emerge in the interactions of the discussions. The one direction that we will provide will be to keep moving towards identifying specific instances of researchable knowledge gaps. We will also ask for everyone's help in extracting from the discussions those key strategic concepts that can help in the management of future pandemic events.

**10:00**           **Coffee and Informal Discussion**

**10:30**           **Researchable Knowledge Gaps**

**12:00**           **Lunch**

**12:45**           **Strategic Concepts for Managing Future Pandemics**

**2:15**            **General Wrap Up and Plans for Preparation of the Task Force Report**

**3:00**            **Adjourn**