

Pandemic Influenza: The Critical Issues and North Carolina's Preparedness Plan

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A Brief Primer

Influenza pandemics have been recorded throughout human history, on average occurring three times in a century, with ten in the last 300 years. Influenza pandemics are simultaneous worldwide epidemics and occur when a new influenza virus evolves that infects humans, is spread efficiently from person-to-person, and because of no prior immunity causes severe disease and death. Between pandemics, called the inter-pandemic period, the milder seasonal influenza (also known as the "flu") exists in the wintertime months in populations living outside of the tropical zones, whereas in the tropics, influenza is a year-around disease. Seasonal viruses are adapted pandemic strains that have weakened mainly due to developed immunity in the human population.

Influenza is characterized by the abrupt onset of fever, chills, muscle pain, and joint pain, followed within hours by respiratory symptoms including cough and congestion. It is a disease primarily of the upper respiratory tract, which in uncomplicated cases resolves in about a week. Complications include bronchitis, pneumonia (both primary viral and secondary bacterial), heart inflammation (myocarditis), and brain inflammation (encephalitis); death can result from any of these complications. In a typical season in the United States, 36,000 people die of influenza, deaths occurring chiefly among infants and the elderly.

The type A influenza virus is unique among viruses because it allows for genetic recombination to occur by the exchange of any or all of its eight gene segments of two different influenza virus strains. Additionally, the influenza virus can mutate and gradually adapt to new environments. Such recombination and adaptation in type A influenza viruses are the cause of pandemics.

Type A virus subtypes are named by the viral surface proteins, hemagglutinin (HA)

and neuraminidase (NA), which elicit an immune response, and thus, comprise major components of the influenza vaccine. In nature, 16 HA and 9 NA proteins exist; however, the human pandemic and seasonal viruses have contained only the subtypes, H1, 2, or 3 and N1, 2, or 3.

The Animal-Human Interface: Zoonotic Influenza

Only type A influenza virus is capable of infecting a broad host range, primarily water fowl and shore birds. Wild water fowl usually harbor type A influenza in their digestive tract and have no symptoms. Spread to other susceptible hosts, usually related species like domestic poultry, happens directly with species intermingling or indirectly via contact with contaminated surface water because type A influenza virus can survive in fresh water for days to weeks.

Type A influenza virus is a type of infectious disease that is transmittable under natural conditions from vertebrate animals to

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humans, also called “zoonosis.” Zoonoses are usually sporadic; however, they are also the origins of epidemics and pandemics. If a human is exposed to an infectious agent from another animal, an infection results if the person is susceptible. Disease may range from asymptomatic to severe, resulting in immunity and recovery or death. An epidemic or pandemic erupts when the disease microorganism adapts via genetic mutation to the new human host and becomes capable of human-to-human transmission. Notorious examples of recent zoonotic-origin pandemics include the human immunodeficiency virus (HIV), the cause of AIDS (from chimpanzees in West Africa),¹ and the severe acute respiratory syndrome (SARS)-coronavirus (from bats in Southeast Asia).²

Type A influenza viruses are often the source of sporadic zoonotic infections, most often from avian, or bird, viruses. Humans are exposed to avian influenza viruses in developing countries across Eurasia and Africa due to animal husbandry practices that involve close contact with diseased or dead domestic fowl, especially ducks and chickens. In developed countries, zoonotic influenza infections have occurred in commercial poultry workers managing infected flocks.

Not all zoonotic influenza cases are of avian origin. In 1976, several soldiers at Fort Dix, New Jersey developed infections, some fatal, from a type A swine influenza virus. It is unknown how these individuals were exposed to a swine virus; however, this cluster led some scientists and policy makers to the false conclusion that this was the harbinger of the next pandemic. It was from this event that the infamous “Swine Flu” vaccination program emanated.

Contemporary methods in the study of human viruses provide information about influenza viruses dating back to 1889. The four pandemics between 1889 and 1968 were of avian origin, and they differed only in the number of avian influenza genes present in the pandemic strain (Table 1).

Table 1.
Hypothesized Evolution of Pandemic Influenza A Viruses³

Pandemic	Subtype	Avian Genes
1889	H2N2	?
1918 “Spanish”	H1N1	8
1957 “Asian”	H2N2	3 (PB1, * HA, NA)
1968 “Hong Kong”	H3N2	2 (PB1, HA)

* PB1 is a viral gene encoding a replication enzyme

H5N1: The Next Pandemic?

In the last 50 years, the science of influenza has made many great strides. In addition to the molecular study of the virus, worldwide human and animal surveillance and the study of population health have greatly expanded. The World Health Organization (WHO) has devoted huge resources to influenza monitoring and study. WHO coordinates the global influenza laboratory surveillance network that characterizes circulating human seasonal virus strains. This information is used to determine the annual human vaccine.

Through this global network, human disease due to avian influenza strain H5N1 was first reported in Hong Kong in 1997. Because this was an avian strain capable of causing severe infections in humans (six of 18 cases reported were fatal), WHO increased the pandemic alert level to Phase 3 (Table 2). Virtually all Hong Kong chickens were slaughtered in an attempt to eradicate the virus. This appeared to have been successful because no further clusters of H5N1 in people or domestic poultry were reported for several years. However, beginning in December of 2003, outbreaks in poultry and humans were reported in Vietnam and Thailand, and through 2006 human reports have increased across Eurasia and Africa with an alarming 60% case-fatality rate (Figure 1).

Table 2.
WHO Pandemic Phases

Period	Phase	Event
Interpandemic	1	No new subtype in humans
	2	No new subtype in humans, animal subtype poses risk
Pandemic alert	3	Human infections with new subtype, no human-to-human spread
	4	Small clusters of limited human-to-human spread
	5	Larger human clusters, but spread still localized
Pandemic	6	Increased and sustained transmission in the general population

H5N1 is currently widespread in wild and domestic birds in Eurasia and Africa with sporadic and often fatal cases in humans. It has notched up the WHO pandemic alert system to Phase 3 since 1997 and satisfies all but one important property of a pandemic-causing influenza virus (Figure 2). Will H5N1 mutate and become capable of efficient human-to-human transmission?

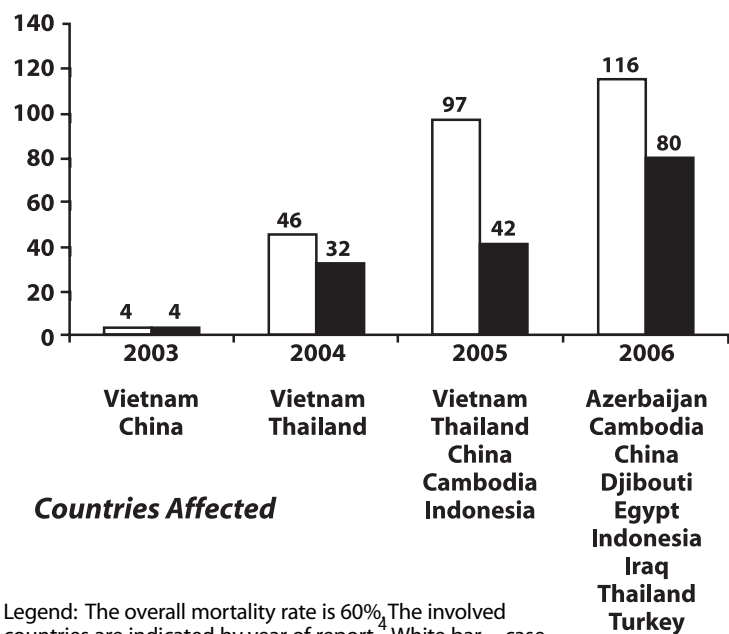
The Present Threat: When, Not If

If we know that pandemics are of avian origin and that they occur cyclically, on average three times in a century, then the question is when will the next avian influenza virus emerge that will cause the next pandemic? Certainly, H5N1 is the leading candidate. In regards to preparation, several subquestions can be generated that assist planning for the next pandemic:

- When will the virus arrive and spread?
- How much time from its source to arrival in the United States or North Carolina?
- What will the principal age and other risk groups be?
- How many will be affected?
- What will be the morbidity?
- What will be the mortality?

In terms of transmission dynamics or spread, nothing is more concerning to an epidemiologist than a community respiratory

Figure 1.
Epidemiological Curve of Reported H5N1 Human Cases
by Reporting Country, 2003-2006."



virus. Transmitted through respiratory droplets from a cough or a sneeze, or direct contact from a person's hands, these viruses can literally spread like wildfire through a susceptible population. The basic reproductive number, R_0 , pronounced "R-zero" or "R-naught," is the expected number of people a contagious person could infect during the infectious period.⁶ An R_0 greater than 1 ($R_0 > 1$) results in a self-sustaining outbreak until there are no more exposed susceptible people. In prevaccination days, a community respiratory virus like mumps with a short incubation period and an $R_0 = 6$ would literally burn through a school-age population.

Influenza virus with an incubation period of 1-5 days and $R_0 = 3$ moves quickly through a community as well. With seasonal influenza, however, R_0 is proportionately reduced by population immunity. For example, if half of the population is immune (from natural infection or vaccination) in a given season, $R_0 = 1.5$.⁶ In a pandemic, however, potentially everyone is susceptible and, at least in the beginning, there will be no vaccine, thus the wildfire analogy.

Worse Case Scenario: A Syndemic

It behooves planners to assume the worst, and for pandemic influenza, that would be a 1918 "Spanish flu"-like pandemic. Worldwide, the second epidemic wave (there were three waves) of the Spanish flu, caused by an H1N1 subtype,

swept across the globe with amazing speed and destruction. In its wake, 50 million people died; in the United States the death toll was 500,000 during the later summer and fall of 1918. Equally disturbing were the high attack and mortality rates that occurred in previously well people in the second and third decade of life, quite unusual for influenza that usually kills the very young and very old.

Historical accounts of young adult victims of the Spanish flu revealed a rapid death due to respiratory failure. People were well one day and dead the next, with facial cyanosis (blue discoloration from lack of oxygen) and a rapid breathing pattern occurring in the hours before death (a condition we now call the acute respiratory distress syndrome or ARDS). Examination of diseased lung tissue showed air sac damage from viral pneumonia. The body's response to the pneumonia caused leaks in the air sacs, drowning the victims (non-cardiogenic pulmonary edema).

In preparing for the next pandemic, it would be helpful to understand why the Spanish flu was so catastrophic. Certainly one reason was the virus itself. The second wave virus has been reconstructed from 1918 victims' lung tissue (both from exhumed remains frozen in the Alaskan tundra and lung

tissue preserved from an autopsy sample).⁷ The reconstructed 1918 virus was found to be highly lethal in the mouse model following intranasal infection. Genetic sequencing revealed it to be a zoonotic type A influenza virus strain whose entire genetic makeup was from a mutated bird strain. This truly novel virus adapted to the new human host acquiring the capability, through evolution, to spread efficiently from person-to-person.

However, in understanding the calamity of 1918, a separate analysis of the social milieu is required, specifically exploring the agents of human activity existing at the time. Historian and author John M. Barry carefully chronicles the global situation in 1918, particularly as the United States prepared for World War I.⁸ Barry's meticulous research of influenza death records and outbreaks associated with massive troop deployments, staging, and overcrowding is compelling. Epidemics in Boston and Philadelphia were traced to ill troops arriving from overseas and

Figure 2.
Checklist of Pandemic Properties of Avian Influenza Type A/H5N1⁵

- ☒ Widespread prevalence in migratory birds; broad host range
- ☒ Continued outbreaks among domestic poultry
- ☒ Mammalian infection (cats, pigs, etc.) lethal
- ☒ Virus is evolving
- ☒ Sporadic human cases
 - Most in young and healthy
 - Case-fatality 60%
 - Rare person-to-person transmission
- ☐ Sustained and rapid person-to-person transmission

an overcrowded patriotic street parade, respectively. Many more examples are cited and all are consistent with massive human crowding and/or movement in the presence of a virulent respiratory virus. In epidemiologic terms, in some settings (barracks, troop ships, etc.), a virus reproductive number (R_0) of 5 or higher was common. Thus, the sociologic and biologic conditions in 1918 formed the perfect storm, a syndemic.

A syndemic is defined as “two or more afflictions, interacting synergistically, contributing to excess burden of disease in a population.”⁹ The term was first used by anthropologist Merrill Singer describing the HIV epidemic among the urban poor in the United States: the SAVA syndemic, for substance abuse, violence and AIDS.¹⁰ He described a new virulent infectious virus, HIV also of zoonotic origins,¹ which spread efficiently by needle sharing intravenous drug abuse and unprotected sexual behavior that wrecked havoc among the poor, particularly in urban minority communities in the United States.

For 21st century pandemic influenza planning, then, I argue that to prevent a 1918-like scenario, we must do syndemic planning. Taking examples from recent natural disasters, such as the 1995 Chicago heat wave that killed 700 elderly people in a week,¹¹ the 2005 tsunami in Indonesia, Hurricane Katrina in New Orleans, or the SAVA syndemic, the common lesson learned is that the natural disaster impact, whether in a developing nation or the United States, is greatly multiplied by crowding and poverty. In 1918, the global population was 1.8 billion; today it is 6.5 billion, 2.7 billion (42%) living in moderate to extreme poverty as measured by income less than \$2/day.¹²

The syndemic model predicts that the next influenza pandemic will be catastrophic in countries such as India and China where 36% of the world population lives, many in poverty and in crowded urban areas. Although these sociologic conditions exist in some areas in the United States and North Carolina, more worrisome in developed countries are the equally vulnerable including those without health insurance or who are underinsured; those who lack the capacity to access information due to illiteracy, low English-speaking skills, and other forms of social isolation; and finally, select special populations such as the homeless, institutionalized, and the underserved mentally ill.

If a 1918-like influenza virus causes the next pandemic, how our nation and state mitigate the impact will depend on pandemic and syndemic prevention. To accomplish this, at the national, state, and local level, public health is leading the planning efforts for the health care sector, government, and society.

Summary of North Carolina's Pandemic Influenza Preparedness Efforts

The fundamental objective of pandemic influenza planning is to save lives. To be successful, all corners of society must plan, including individuals and families, business and industry, schools and universities, and state and local government. These overarching plans, referred to as pandemic implementation strategies, are underway or complete in many sectors, but beyond the scope of this review. Here, I will highlight the critical components of *North Carolina's Public Health Pandemic Influenza Plan*.¹³

Quenching

In public health, prevention is the key, thus a critical strategy is the early detection of initial outbreaks and rapid containment of the disease where it emerges, a process known as quenching.¹⁴ Through global and national collaboration with the WHO and the Centers for Disease Control and Prevention (CDC), once an influenza pandemic is declared somewhere in the world, the North Carolina Division of Public Health (DPH) will enhance frontline detection and response and rapid laboratory diagnosis. The early cases in North Carolina will likely be among travelers to regions where person-to-person transmission is ongoing.

In WHO pandemic phases 4, 5, and early 6, international travel advisories will be issued by federal authorities. DPH will notify health care providers of the situation and explain how to suspect and manage patients who may be manifesting pandemic influenza symptoms. Suspect patients shall be reported immediately to local or state public health agencies (North Carolina General Statute 130A-135), isolated (NCGS 130A-145),¹⁵ and treated with antiviral medication pending laboratory confirmation. The North Carolina State Laboratory for Public Health will activate three regional labs in Charlotte, Asheville, and Greenville, as well as the core facility in Raleigh, to rapidly (within hours) process clinical specimens (nasopharyngeal swabs) for detection of the pandemic strain. These labs will not attempt to cultivate pandemic viruses because of the biosafety hazard; cultural confirmation will be done solely by the CDC in Atlanta, Georgia.

The goal of quenching is for public health and other response agencies to aggressively keep the $R_0 < 1$. Once a suspected patient has been reported to public health agencies, active surveillance will begin to identify close contacts (eg, airplane passengers, household and workplace contacts). If an index case is presumptively confirmed by the labs, symptomatic contacts will be isolated and referred for medical evaluation and asymptomatic contacts will be quarantined for 10 days (or the maximum incubation period) from the time of last contact to a case. Based on what is known about the contagiousness and virulence of the pandemic virus, quarantined people may be offered antiviral prophylaxis at no cost from a federal or state stockpile. Antiviral prophylaxis of exposed contacts in quarantine may be the single most effective strategy in preventing a full-blown pandemic, an $R_0 > 1$.

Isolation and quarantine are restrictions of movement and/or action of the sick (isolation) and the well but exposed (quarantine). An effective quenching plan requires rapid active surveillance and diagnosis, treatment or post-exposure prophylaxis with antivirals, and enforcement of isolation and quarantine. During the 2003 SARS response in North Carolina confirmation of a single case led to the isolation of three persons and the quarantine of 30 others. All affected people complied with local public health authorities, law enforcement was not necessary, and the spread was contained.

WHO Phase 6: Widespread Pandemic in North Carolina

Planning assumptions identify a point in time when quenching fails or is no longer feasible. This may happen if there are multiple simultaneous outbreaks across the state, a local jurisdiction's capacity to quench is overwhelmed and there are no state or federal assets available to assist, or supplies of antiviral medications are depleted leaving enough only to treat the sickest. To decrease illness and death, the strategy at such a point will be to slow the spread and buy time until an influenza pandemic vaccine is available. To accomplish this, countermeasures known as nonpharmaceutical and pharmaceutical interventions will be used.

Nonpharmaceutical Interventions

The nonpharmaceutical intervention for preventing or slowing a pandemic is the physical separation of people. This is accomplished in fundamentally two ways: personal protective equipment for those who must be close to the sick (health care workers, first responders) and social distancing and hygiene. The worst-case scenario is that 50% or more of those who become ill will seek medical care. The number of hospitalizations and deaths will depend on the virulence of the pandemic virus and Table 3 projects these numbers based upon the experiences of the moderate and severe pandemics of 1957 and 1918. Depending on severity, health care medical surge plans must scale accordingly, the largest challenge being the maintenance of adequate staffing. To provide for the safety of those on the frontline, occupational health protection through infection control is a critical planning component. In hospitals, respiratory droplet and airborne precautions that are part of everyday activity will be essential during a pandemic. For routine patient care, properly donned and doffed eye protection and a plain surgical mask are adequate along with hand washing with soap and water before and after patient contact. For higher risk contact where infectious aerosols are more likely to be generated (eg, airway suctioning, resuscitation, bronchoscopy), a fit-tested N-95 respirator is required. In the community, there is no evidence that personal protective equipment, such as the donning of masks by well people, will prevent transmission of influenza. Hence, stockpiling masks or respirators outside of the health

care setting is not recommended and is not part of the *NC Pandemic Influenza Plan*.

The broader community containment strategy will rely on social distancing interventions. In WHO Phase 6 for a moderate to severe pandemic, at some threshold a state of emergency will be declared where so-called mass quarantine will be utilized. Mass gatherings including entertainment venues like sporting events and theaters will be canceled or closed, religious services will be discouraged or prohibited, nonessential workers will be told to remain at home, and schools and universities will be closed. In 1918, the city of St. Louis implemented these measures and succeeded in reducing influenza-related mortality. Indeed, government may not need to impose these measures because individuals are likely to self-quarantine if the pandemic is bad enough.

The societal disruptions will be immense, but can be lessened by cross-sector preparation. Continuity of operations planning is the core of the national implementation strategy and is essential for critical industries such as utilities, businesses, educational institutions, and government.

Pharmaceutical Interventions

Pharmaceutical interventions refer to the specific countermeasures for prevention and treatment of influenza A infections: antiviral medications and vaccines. The planning assumption for antivirals is that they will be effective in the treatment and prevention of pandemic influenza. Although clinical trials will be difficult to conduct against the current H5N1 threat, there is accumulating evidence that these drugs will have broad-spectrum activity against pandemic influenza.¹⁶ The current federal government guideline calls for the stockpiling of enough antiviral medications to treat 25% of the population, roughly two million five-day courses for North Carolina. The stockpiling challenges lie in accumulating an adequate supply to meet the need, establishing rationing criteria until the supply is adequate, and extending the shelf-life beyond five years.

Assuming the antiviral medications are found to be life-saving and the supply is inadequate at the time of the pandemic, then difficult rationing decisions will have to be made. To ensure fairness and equity and to assist frontline providers, the *NC Pandemic Influenza Plan* aligns with the federal tier groups to receive antiviral treatment in the event of suspected influenza illness only.¹⁷ The top five tier priority groups to receive treatment are hospitalized patients, health care workers and emergency medical technicians, high-risk outpatients including the immunocompromised and pregnant women, public health responders (eg, vaccinators, vaccine and antiviral manufacturers, government decision makers) including public safety (police, fire, and corrections), and increased risk outpatients (children 12-23 months, adults aged 65 years and above, and people with chronic medical conditions). To reiterate, this rationing scheme is for treatment only; it is assumed during a widespread WHO phase 6 event, there will not be enough medication for prevention.

The second pharmaceutical intervention is a pandemic vaccine, which can abort the pandemic once available for the

Table 3.
Impact of an Influenza Pandemic in North Carolina*

Characteristic	Moderate (1957-like)	Severe (1918-like)
Illness	3,000,000	3,000,000
Outpatients	1,600,000	1,600,000
Hospitalized	35,000	300,000
Deaths	8,000	65,000

* Numbers based on NC population = 9,000,000; 35% attack rate (CDC FluAid 2.0)

entire population. The planning assumption, however, is that it will probably take a year or more to scale up production to immunize everyone. Further, because the population will be naïve to the pandemic virus, a booster shot will be required one month after the priming dose. Thus, once again, rationing of the first supplies of the pandemic vaccine is a planning component aligning with federal tier groups.¹⁷ In Tier 1, there are four subtiers who will get the vaccine first:

- 1) Vaccine and antiviral manufacturers, essential medical and public health workers;
- 2) High-risk persons (> 65 years old, medical co-morbidities)
- 3) Pregnant women, household contacts of severely immunocompromised, household contacts of children < 6 months old;
- 4) Public health emergency response workers, key government leaders.

Syndemic Prevention: Preparedness and Communication

Ultimately, how North Carolina responds to a severe influenza pandemic will depend upon countermeasures applied equitably to all who reside in the state. Since human beings are the vector and reservoir of the disease, neglecting or limiting resources to any sector of society (outside of established

rationing protocols) does not make any epidemiologic sense. In addition, it is unrealistic to believe that society can mitigate the syndemic conditions of crowding, poverty, and the needs of special populations in advance of a rapidly moving pandemic wave. How do we approach this daunting challenge?

The impact of a pandemic or any disaster is proportional to how prepared individuals and society are. Preparedness is a shared responsibility that requires local, state, and federal public health systems to form a robust response network. Implementation strategies must build international and domestic, animal and human health, and public and private sector partnerships. Health, security, and economic protection are at stake, and all these risks should be managed cooperatively.

Syndemic prevention will rely on our ability to reach those outside of traditional networks, and to accomplish this, clear communication channels must be established to the public using trusted messengers. Health disparities during a disaster are preventable if people are prepared with accurate and timely information. How well public health is able to coordinate consistent messages, encourage people to take action steps to prepare now, and provide updates when new information becomes available will determine how we weather the perfect storm. **NCMJ**

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