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Avian Influenza (H5N1) and Pandemic Influenza What Every Virginia Healthcare Professional Should Know

Adapted from the U.S. Department of Health and Human Services *Pandemic Influenza Plan*, November, 2005.[1]

Introduction

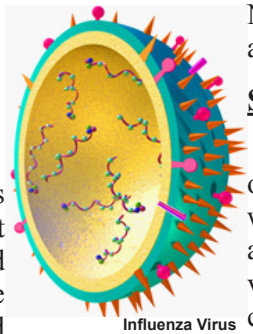
The 20th century saw three influenza pandemics, including the 1918 Spanish Flu (H1N1) that caused over 500,000 deaths in the U.S. and an estimated 50 million deaths worldwide. A comparable pandemic in 2005 would cause almost two million deaths in the U.S. alone. It has been 37 years since the last pandemic, and many scientists believe that it is only a matter of time until the next occurs.[2]

The recent emergence of highly pathogenic avian influenza A (H5N1) in Asia, with a demonstrated ability to infect and kill humans, has renewed concern that an influenza pandemic may be imminent. If the virus acquires the ability to sustain person-to-person transmission, it could rapidly spread worldwide. Since healthcare professionals would play an essential role in the detection and management of an influenza pandemic, they require up-to-date information on the potential threat from avian influenza, current recommendations for the management of patients with potential novel influenza infection, and an understanding of the efforts at the local, state, and national level to address this issue.

Background

Influenza Virus

There are two main types of influenza viruses that infect humans: "A" and "B". Type A viruses are divided into subtypes based on the specific hemagglutinin (H) and neuraminidase (N) proteins on the virus surface. These proteins affect the pathogenesis of the virus and the host's immune response. The H protein governs the ability of the virus to bind to and enter cells, where multiplication of the virus then occurs. The N protein governs the release of newly formed viruses from the cells. Overall, at least 16 distinct antigenic subtypes of H (H1 to H16) and nine subtypes of N (N1 to N9) have been identified in wild aquatic birds.[1]


Influenza Virus
Credit:NIAID

Seasonal Influenza

Currently, two main subtypes of influenza A viruses circulate worldwide in humans: H3N2 and H1N1. However, influenza viruses within a subtype can change gradually through "an-

tigenic drift," where mutations to the virus genome produce small changes in the viral H or N proteins. Since infection with influenza occurs more commonly in the winter in temperate climates such as the U.S., the appearance and spread of these new strain variants causes a 'seasonal' pattern of epidemics. However, the effects of these new variants are moderated because most individuals have some underlying degree of immunity to the circulating influenza virus subtypes either from previous infection or from vaccination.[1]

Signs and symptoms of influenza infection in humans vary in severity, but generally include a sudden onset of fever, headache, myalgia, prostration, coryza, sore throat, and dry cough. Otitis media, nausea, and vomiting are also commonly seen among children. However, typical influenza (or "flu-like") symptoms may not always be present in elderly patients, young children, patients in long-term care facilities, or persons with underlying chronic illnesses.[1]

For many individuals influenza is not a trivial disease. In the U.S. seasonal influenza epidemics result in approximately 36,000 deaths, 226,000 hospitalizations, and $1-3 billion in direct costs for medical care annually. Secondary complications such as pneumonia, dehydration, and worsening of chronic lung and heart problems cause a significant amount of the disease burden.[1]

Avian Influenza

While influenza A viruses can infect many different animals (including pigs, whales, horses, seals, etc.), wild birds are considered the natural reservoir, because more influenza A subtypes circulate among wild birds than any other species. Wild birds can carry the virus without displaying any symptoms of the disease and can spread the virus over long distances while remaining healthy. Poultry are quite susceptible to avian influenza where the virus can cause manifestations that range from mild (e.g., reduced egg production) to severe (e.g., rapid death). While animal influenza viruses do not normally infect humans, they can sometimes cross over and cause illness (Box 1).[1]

Box 1 – Avian Influenza Outbreaks

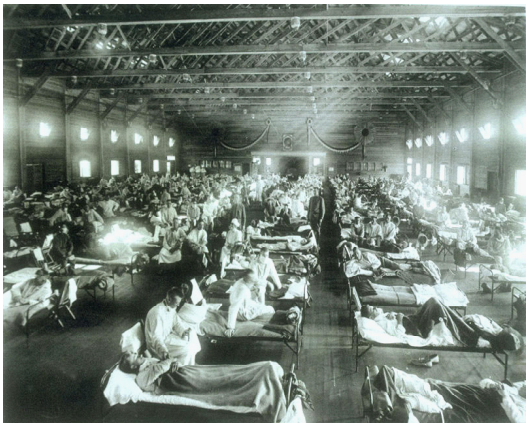
The U.S. Department of Agriculture (USDA) classifies avian influenza viruses as low pathogenic avian influenza (LPAI) viruses or highly pathogenic avian influenza (HPAI) viruses, based on characteristics of the virus or its virulence in birds.[1]

Some examples of LPAI outbreaks include:

- H5N2: poultry outbreaks in NY, ME, and CA in 2002
- H7N2: poultry outbreaks in VA in 2002, and DE, MD, and NJ in 2004
- H9N2: sporadic human cases of ILI in Hong Kong and China in 1998-2003

Examples of HPAI outbreaks include:

- H5N1: major poultry outbreaks and sporadic human cases in Southeast Asia 1997-present
- H7N7: human outbreak in the Netherlands in 2003
- H7N3: human outbreak in British Columbia in 2004
- H5N2: poultry outbreaks in northeastern US in 1983 and TX in 2004



Emergency Hospital, 1918-1919 Influenza

Avian influenza outbreaks create the possibility that a new (novel) virus will develop through "antigenic shift," where either significant mutations or a mixing of genetic material (reassortment) from separate human or animal viruses in a simultaneously co-infected host create a significantly different combination of H and N proteins. Since people do not have pre-existing antibody protection to these new hybrid viruses, the infectivity and severity of the resulting infection then depends on the specific characteristics of the new virus.[1]

While recent avian influenza outbreaks have not produced viruses with the ability to spread easily from person-to-person, a particularly severe subtype of "highly pathogenic avian influenza,"

Table 1. Number of Episodes of Illness, Healthcare Utilization, and Death Associated with Moderate and Severe Pandemic Influenza Scenarios*

Characteristic	Moderate (1958/68-like)	Severe (1918-like)
Illness	90 million (30%)	90 million (30%)
Outpatient medical care	45 million (50%)	45 million (50%)
Hospitalization	865,000	9,900,000
ICU care	128,750	1,485,000
Mechanical ventilation	64,875	742,500
Deaths	209,000	1,903,000

*Estimates based on extrapolation from past pandemics in the United States. Note that these estimates do not include the potential impact of interventions not available during the 20th century pandemics.

influenza A (H5N1), that has been ravaging wild and domestic poultry populations in Asia and Europe since 1997 is causing concern. Virus shed in saliva, nasal secretions, and droppings of migratory waterfowl into commercial and backyard poultry flocks have caused large outbreaks characterized by severe illness (mortality approaches 100% in domestic poultry). From December 2003 to December 9, 2005, eleven Asian countries (Cambodia, China, Indonesia, Japan, Kazakhstan, the Republic of Korea, the Lao People's Democratic Republic, Malaysia, Mongolia, Thailand and Viet Nam) and five European countries (Croatia, Russia, Turkey, Romania, and Ukraine) have identified outbreaks in wild or domestic birds.[3] Attempts at containing the outbreaks have included quarantining infected farms and mass destruction of domestic poultry. This has led to the deaths of millions of chickens and significant financial loss in countries that depend on poultry for income and food. Nevertheless, the influenza A (H5N1) virus has become endemic in many parts of Asia and continues to spread along wild bird migratory paths.[4]

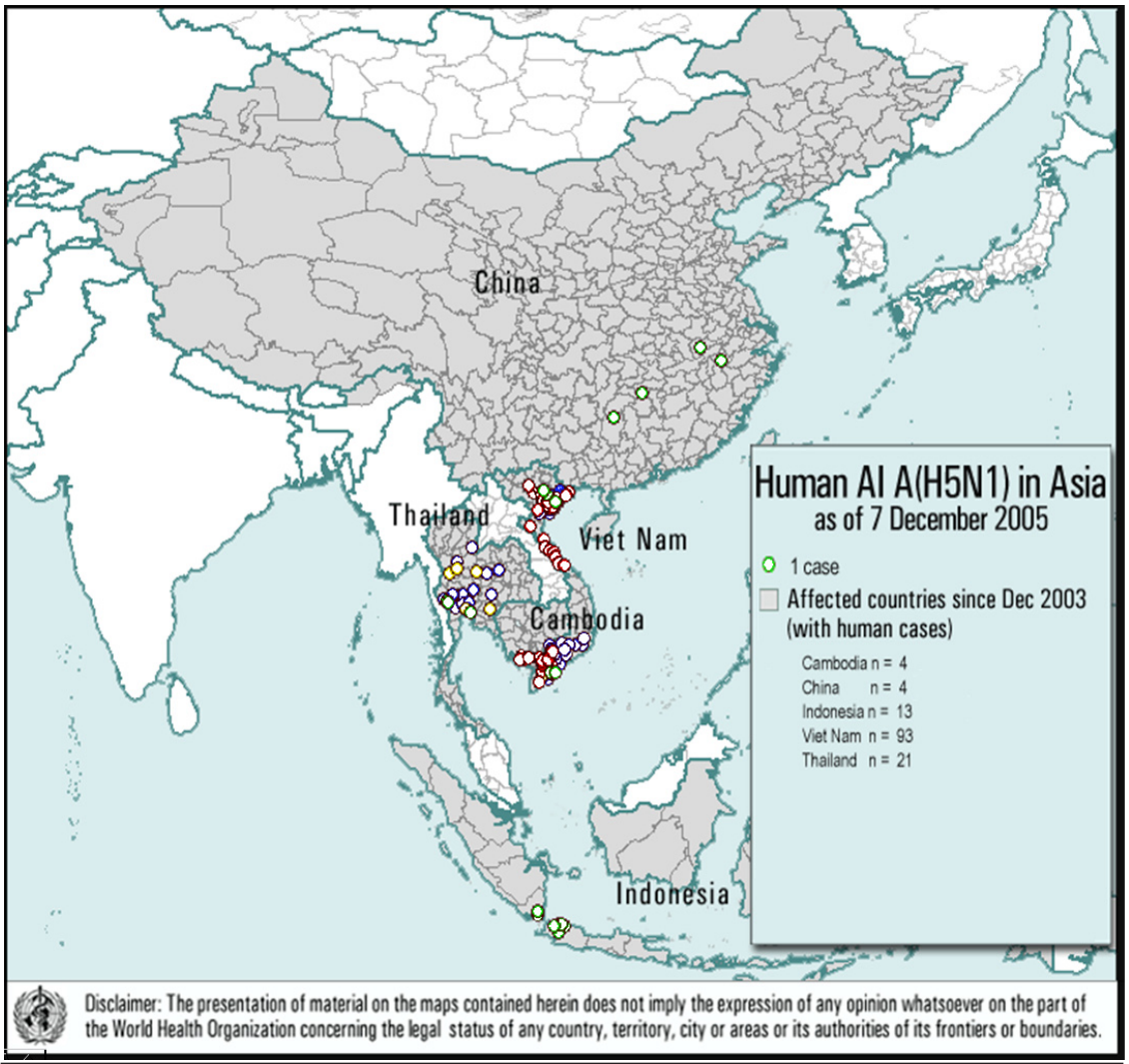


Figure 1: Adapted from WHO:www.wpro.who.int/NR/rdonlyres/DDAADCFE-09E7-4A2B-A1F1-2B6FD9B103F7/0/700_1207.gif

In addition, unlike other recent avian influenza outbreaks, significant numbers of human cases of influenza A (H5N1) infection have been reported. The 1997 outbreak in Hong Kong resulted in 18 known human cases with six deaths. In addition, molecular studies suggest direct bird-to-human transmission occurred (prior to this outbreak it was believed that an intermediate host was required for humans to contract an avian influenza virus). The outbreak ended after authorities slaughtered Hong Kong's entire stock of poultry (about 1.5 million birds).[4]

However, the spread of influenza A (H5N1) virus in wild and domestic birds has continued to cause sporadic cases in humans. As of December 7, 2005, a total of 135 laboratory-confirmed human cases of influenza A (H5N1), causing 69 deaths, have been reported in Cambodia, China, Indonesia, Thailand and Viet Nam (see Figure 1).[5] [Note: accurately calculating a case fatality rate is not possible because authorities do not know how many people have had milder cases but did not seek medical care or how many received care that was not reported].[4] Almost all human infections to date have been linked to contact with infected poultry, although isolated instances of human-to-human transmission following close contact with a patient during the acute phase of illness may have occurred.[6]

Clinical descriptions of human illness with influenza A (H5N1) infection have been based on hospitalized cases. Cases have generally been previously healthy children or young adults who present with high fever (>38°C) and a primarily lower respiratory tract illness (cough, dyspnea) that progresses to severe disease in a high proportion of cases. Upper respiratory symptoms, such as sore throat or rhinorrhea have been rare. Respiratory distress, tachypnea, and inspiratory crackles are common. Sputum production is variable and sometimes bloody. Many cases have developed watery diarrhea without blood or inflammatory changes that may precede respiratory manifestations by up to one week. Almost all patients have clinically apparent pneumonia; radiographic changes include diffuse, multifocal, or patchy infiltrates; interstitial infiltrates; and segmental or lobular consolidation with air bronchograms. Complications have included respiratory failure with

acute respiratory distress syndrome (ARDS) and multi-organ failure. Milder illnesses, subclinical infections, and atypical presentations with influenza A (H5N1) virus infection have also been reported.[6]

Pandemic Influenza

Pandemics are world-wide epidemics of a disease. Influenza pandemics typically occur three to four times a century. For example, in the 20th century the 1918 ("Spanish flu") pandemic resulted from the emergence and spread of the influenza A (H1N1) virus, while the 1968 ("Hong Kong flu") pandemic was associated with the influenza A (H3N2) virus. The 1957 ("Asian flu") pandemic was associated with the emergence and spread of the influenza A (H2N2) virus; however, this virus subtype stopped circulating in 1968.[1]

Although a **novel** influenza virus (resulting from genetic mutation or reassortment) could emerge from anywhere in the world at any time, scientists are particularly concerned about the avian influenza A (H5N1) virus circulating in Asia and parts of Europe.[1] The relatively low frequency of influenza A (H5N1) illness in humans despite widespread exposure to infected poultry indicates a substantial species barrier.[6] However, sustained transmission in humans is the only remaining step needed for this virus to have the ability to cause a pandemic. The more widespread this strain becomes, the higher the probability of a pandemic. As a result, the World Health Organization defines the current situation as Phase 3 of a "Pandemic Alert Period" (Box 2).[7]

Box 2 - WHO Global Pandemic Phases[8]
Interpandemic Period
Phase 1. No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low
Phase 2. No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease
Pandemic Alert Period
Phase 3. Human infection(s) with a new subtype but no human-to-human spread or at most rare instances of spread to a close contact
Phase 4. Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans
Phase 5. Larger cluster(s) but human-to-human spread is still localized, suggesting that the virus is becoming increasingly better adapted to humans but may not yet be fully transmissible (substantial pandemic risk)
Pandemic Period
Phase 6. Pandemic phase: increased and sustained transmission in the general population
Postpandemic Period
Return to the Interpandemic Period (Phase 1)

Clinical Aspects of Novel Influenza

Human influenza viruses circulate worldwide and year-round, including in countries with outbreaks of avian influenza A (H5N1) among poultry. Clinicians face significant challenges in: 1) quickly identifying and triaging cases, 2) containing the spread of infection, 3) beginning an efficient and comprehensive workup, 4) initiating antiviral and other supportive therapy, and 5) anticipating clinical complications.[1]

Currently (as of November, 2005) returned travelers with influenza-like illness (ILI) are more likely to have infection with human influenza virus than with avian influenza A (H5N1) virus. To limit the need to evaluate an overwhelming number of patients, specific screening criteria for evaluation that rely on a combination of clinical and epidemiologic features have been developed:

A. Criteria for evaluation of patients with possible novel influenza

The following criteria are based on the features of recent influenza A (H5N1) cases but are intended for use in evaluating suspected cases of infection with any novel influenza A virus strain. During the Pandemic Alert Period, **both clinical and epidemiologic criteria should be met***:

Clinical criteria^

Temperature of >38°C (>100.4°F)

plus at least **one** of the following:

- Sore throat;
- Cough; or,
- Dyspnea.

Note: Should the next pandemic influenza virus strain present with a different clinical syndrome the clinical criteria will be modified accordingly and posted at www.cdc.gov/flu.

Epidemiologic criteria

Travel risks:

Within 10 days of symptom onset the patient had visited or lived in an area affected by highly pathogenic avian influenza A outbreaks in domestic poultry or where a human case of novel influenza has been confirmed (a regularly updated listing of influenza A (H5N1)-affected countries is available at www.who.int/en/); *and had either:*

- Direct contact with poultry (well-appearing, sick, or dead). Examples include a visit to a poultry farm, a household raising poultry, or a bird market; consumption of uncooked poultry or poultry products; or direct exposure to environmental

*For persons with a high risk of exposure to a novel influenza virus, epidemiologic evidence might be enough to initiate further measures, even if clinical criteria are not fully met. In these persons, early signs and symptoms (e.g., rhinorrhea, conjunctivitis, chills, rigors, myalgia, headache, diarrhea) may be used to fulfill the clinical criteria for evaluation.[1]

^High-risk groups with atypical symptoms: Young children, elderly patients, patients in long-term care facilities, and persons with underlying chronic illnesses might not have typical ILI signs or symptoms. In such persons with strong epidemiologic risk factors, novel influenza should be considered with almost any change in health status (e.g., conjunctivitis, vomiting/diarrhea, apnea) even in the absence of typical clinical features.[1]

Box 3 - Assumptions about Pandemic Influenza[1]
— Susceptibility to the pandemic influenza subtype will be universal.
— The clinical disease attack rate may be 30% in the overall population. Illness rates will be highest among school-aged children (about 40%) and decline with age. Among working adults, an average of 20% will become ill during a community outbreak.
— Of those who become ill with influenza, 50% will seek outpatient medical care.
— Modeling suggest that about 10% of the workforce will be absent due to illness or caring for an ill family member at any given point in time.
— The number of hospitalizations and deaths will depend on the virulence of the pandemic virus. Estimates, based on extrapolation of past pandemic experience, provide ranges on the actual impact.
— Risk groups for severe and fatal infections cannot be predicted with certainty. Complications from seasonal influenza strike mainly infants, the elderly, persons with chronic illnesses, and pregnant women; in the 1918 pandemic, most deaths occurred in young, previously healthy adults.
— The typical incubation period is likely to average two days.
— Persons who become ill may shed viruses and potentially transmit infection for one-half to one day before the onset of illness. Viral shedding and the risk for transmission will be highest during the first two days of illness. Children shed the largest quantity of viruses and therefore are likely to pose the highest risk for transmission.
— On average about 2-3 secondary infections will occur as a result of transmission from someone who is ill.
— In an affected community, a pandemic outbreak will last about 6-8 weeks.
— At least two pandemic disease waves are likely. Following the pandemic, the new viral subtype is likely to continue circulating and to contribute to seasonal influenza.

contamination with poultry feces; *or,*

— Close contact with a person with suspected or confirmed novel influenza infection.

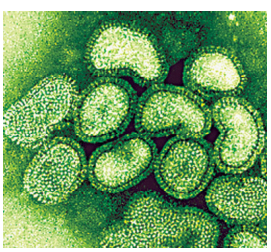
Occupational risks:

Working on poultry farms or in live poultry markets; processing or handling poultry infected with known or suspected avian influenza viruses; working in laboratories that contain live animal or novel influenza viruses; providing healthcare to a suspected or confirmed novel influenza case.

B. Initial management of patients who meet the criteria for novel influenza

When a patient meets **both the clinical and epidemiologic criteria** for a suspected case of novel influenza during the current Pandemic Alert Period, healthcare personnel should initiate the following activities:

► **Implement infection control precautions** for novel influenza, including a combination of standard, contact, droplet, and airborne isolation precautions [e.g., high-efficiency masks (NIOSH-certified N-95 or equivalent), long-sleeved cuffed gowns, face shield or eye goggles, and gloves].[6] Precautions should be in place for seven days after the resolution of fever, but may be necessary for up to 21 days or until another etiology has been identified before that period has elapsed.[1,6]



The decision to hospitalize a suspected novel influenza case will be based on the physician's clinical assessment (including severity of illness, patient resources, and risk for complications). Hospitalized patients who may be infected with novel influenza virus should be housed in a negative-pressure room, if available, or in a single room with the door closed.[6] Patient movement and transport within the hospital should be limited to medically necessary purposes.[1]

For outpatient management, local health department staff can assist in providing recommendations on adequate precautions to prevent the potential spread of infection in the home and community.[1]

► **Notify the local health department**. Report suspected cases of novel influenza to the local health department as quickly as possible to facilitate initiation of public health measures. Designate one person as a point of contact to update public health authorities on the patient's clinical status.[1]

► **Contact the Virginia Division of Consolidated Laboratory Services (DCLS) and the local health department to obtain information about proper specimen collection, shipping, and testing for novel influenza.** For novel influenza testing, DCLS can be contacted 24/7 by paging 804-418-9923. General guidelines for specimen collection are provided in the national pandemic influenza plan (Supplement 2, Appendix 5). However, DCLS should be contacted before specimen collection to assure proper collection, biocontainment, transport, and testing. Clinical laboratories should not attempt virus isolation, unless performed in biosafety level BSL-3 with enhancements and

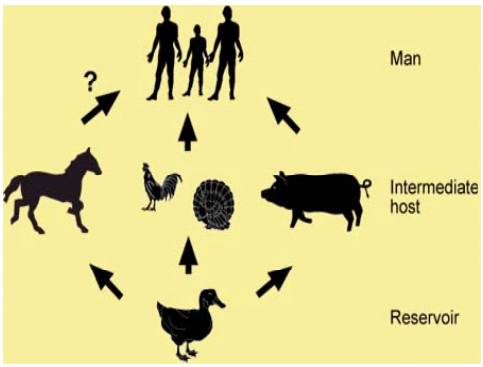
separate from areas where seasonal influenza virus is cultured. Specimens submitted from patients suspected of novel influenza virus infection must be clearly labeled so that laboratory workers can follow appropriate biosafety guidelines (national pandemic influenza plan, Supplement 2, Appendix 4).

Rapid influenza diagnostic tests [e.g. commercial antigen detection of influenza by enzyme immunoassay (EIA)] may be conducted under BSL-2 conditions if a Class II biological safety cabinet is used. During a pandemic, rapid diagnostic tests will be widely used to distinguish influenza A from other respiratory illnesses. However, clinicians should be reminded that a negative test result might not rule out novel influenza virus infection and should not affect patient management or infection control decisions. Guidance about the reliability and interpretation of rapid influenza test results is provided in the national pandemic influenza plan (Supplement 2, Appendix 6).

► **Evaluate alternative diagnoses.** The fever and respiratory manifestations of seasonal influenza are not specific and can occur with several other pathogens, including respiratory syncytial virus (RSV), parainfluenza viruses, adenoviruses, human metapneumovirus, rhinoviruses, coronaviruses, and *Mycoplasma pneumoniae*. In contrast to influenza viruses, most of these pathogens do not usually cause severe disease, particularly in previously healthy adults. RSV and parainfluenza viruses can, however, lead to severe respiratory illness in young children and the elderly and should be considered in the differential diagnosis if circulating in the community.

Depending on the clinical presentation and the patient's underlying health status, other testing may include:

- —Pulse oximetry
- —Chest radiograph
- —Complete blood count with differential



- —Blood cultures
- —Gram stain and culture of sputum (in adults), tracheal aspirate, and pleural effusion aspirate (if present)
- —Antibiotic susceptibility testing for any bacterial isolates
- —Multivalent immunofluorescent antibody testing or PCR of nasopharyngeal aspirates or swabs for common viral respiratory pathogens (e.g., influenza A and B, adenovirus, parainfluenza virus, respiratory syncytial virus)
- —If radiographic evidence of pneumonia, *Legionella* and pneumococcal urinary antigen testing
- —*Mycoplasma pneumoniae* and *Chlamydia pneumonia* testing (e.g., PCR), if available
- —Serum chemistry panel

If an alternate etiology is identified, the possibility of co-infection with a novel influenza virus may still be considered if there is a strong epidemiologic exposure link to novel influenza.[1]

► **Initiate antiviral treatment** as soon as possible, even if laboratory results are not yet available. The clinical effectiveness of antiviral drugs for the treatment of novel influenza infections is unknown, but it is likely that the earlier treatment is initiated, the greater the likelihood of benefit. During the Pandemic Alert Period, available virus isolates from any case of novel influenza will be tested for resistance to the currently licensed antiviral medications.[1]

► **Assist public health officials with the identification of potentially exposed contacts.** Clinicians may need to help identify persons exposed to the suspected novel influenza case-patient. In general, persons in close contact with the case-patient at any time beginning one day before the onset of illness are considered at risk. Close contacts might include household and social contacts, family members, workplace or school contacts, fellow travelers, and/or healthcare professionals.[1]

C. Management of patients who test positive for novel influenza

If a patient is confirmed to have an infection with a novel influenza virus, additional input from federal, state, and local public health authorities will be needed. In general, healthcare personnel would continue antiviral treatment and all isolation and infection control precautions, including isolation of patients with novel influenza from seasonal influenza patients (to decrease the risk of co-infection and viral genetic reassortment).[1]

D. Management of patients who test negative for novel influenza

The sensitivity of the currently available tests for detecting novel influenza viruses in clinical specimens has not been thoroughly evaluated with a full range of specimen types. Consequently, false-negative test results may occur. Therefore, the interpretation of negative testing results should be tailored to the individual patient in consultation with hospital infection control and infectious disease specialists, as well as the state or local health department and CDC. If test results are negative but the clinical and epidemiologic suspicion remains high, especially if no alternative diagnosis is available, continued antiviral treatment and isolation procedures should be considered.[1]

When influenza tests are negative and an alternative diagnosis is established, isolation precautions and antiviral drug therapy for novel influenza may be discontinued based on the clinician's assessment.[1]

Public Health Efforts

The Virginia Department of Health (VDH), using the Centers for Disease Control and Prevention (CDC) FluAid

Box 4 – The impact of pandemic influenza

The effects of a flu pandemic are different from many of the public health emergencies that our healthcare system has prepared for in the past.

- Multiple areas will be affected simultaneously and disease will be widespread, making it difficult to borrow resources from the few unaffected areas.
- The pandemic will last for months in a community, much longer than most emergency situations, and it may come in "waves," or peaks of activity separated by several months.
- Healthcare workers and first responders will be affected, further straining the ability to combat the pandemic.
- Preventive and therapeutic agents, namely vaccine and antivirals, will be in short supply.[2]

2.0 program, has generated estimates of the impact of an influenza pandemic on Virginia. The estimates are based on Virginia population statistics from the 1999 U.S. Census and a projected "gross attack rate" of 15-35% that reflects the percentages of the population with a case of influenza causing some measurable impact (e.g., work time lost, patient visit to a doctor). Detailed projections are posted in the Virginia Pandemic Influenza Response Plan at www.vdh.virginia.gov. However, even a mid-range attack rate of 25% could cause 4,491 deaths, 20,180 hospitalizations, and 956,407 outpatient visits in Virginia over a 24 week period.[8]

An influenza pandemic resulting in such a sudden surge of healthcare needs could overwhelm hospitals and create critical shortages in intensive care facilities, mechanical ventilators, personal protective equipment, and medications. Healthcare personnel will be at high risk of infection and may have significant rates of absenteeism due to illness or the need to care for loved ones at home. Management of the dead may overwhelm morgue and burial capacity. In addition, widespread illness in the community could increase the likelihood of sudden shortages of personnel in other sectors that provide critical public safety and supply services such as food, water, and electricity.

Therefore, adequate preparation for an influenza pandemic includes anticipating the possible effects on Virginia communities so that appropriate interventions may help to reduce morbidity and mortality. Appropriate protective public health measures also need to be developed to reduce person-to-person viral transmission and prevent or delay influenza outbreaks. These include the use of surveillance, immunization, antiviral medications, and individual- and community-based containment measures. Sustained human-to-human transmission of a novel influenza virus anywhere in the world will be the triggering event to initiate a pandemic response by the United States.[1]

Surveillance

Surveillance focuses on collecting influenza viral isolates for testing, monitoring morbidity and mortality, and identifying unusual or severe influenza outbreaks. The U.S. national influenza surveillance system includes: laboratory surveillance, outpatient influenza-like illness (ILI) surveillance, pneumonia and influenza (P&I) related mortality surveillance, and an assessment of influenza activity at the state level. Traditionally, U.S. influenza surveillance has been conducted from October through mid-May, but nationwide surveillance is now being conducted year-round.[1]

Virginia's influenza surveillance has a three-tiered approach to quickly detect outbreaks:

a. Passive component - Includes reports of influenza from physicians, medial care facilities, and laboratories.
b. Active sentinel component - Designated primary care outpatient practices across Virginia report total number of cases of ILI to local health departments each week from October to May. The information is relayed to the state health department to determine the relative level of influenza activity.
c. Laboratory surveillance - The state laboratory (DCLS) identifies various strains of influenza circulating in Virginia from viral culture specimens collected throughout the year. Some of the identified strains are sent to the CDC to be used to guide recommendations for treatment and vaccine development for the next year.

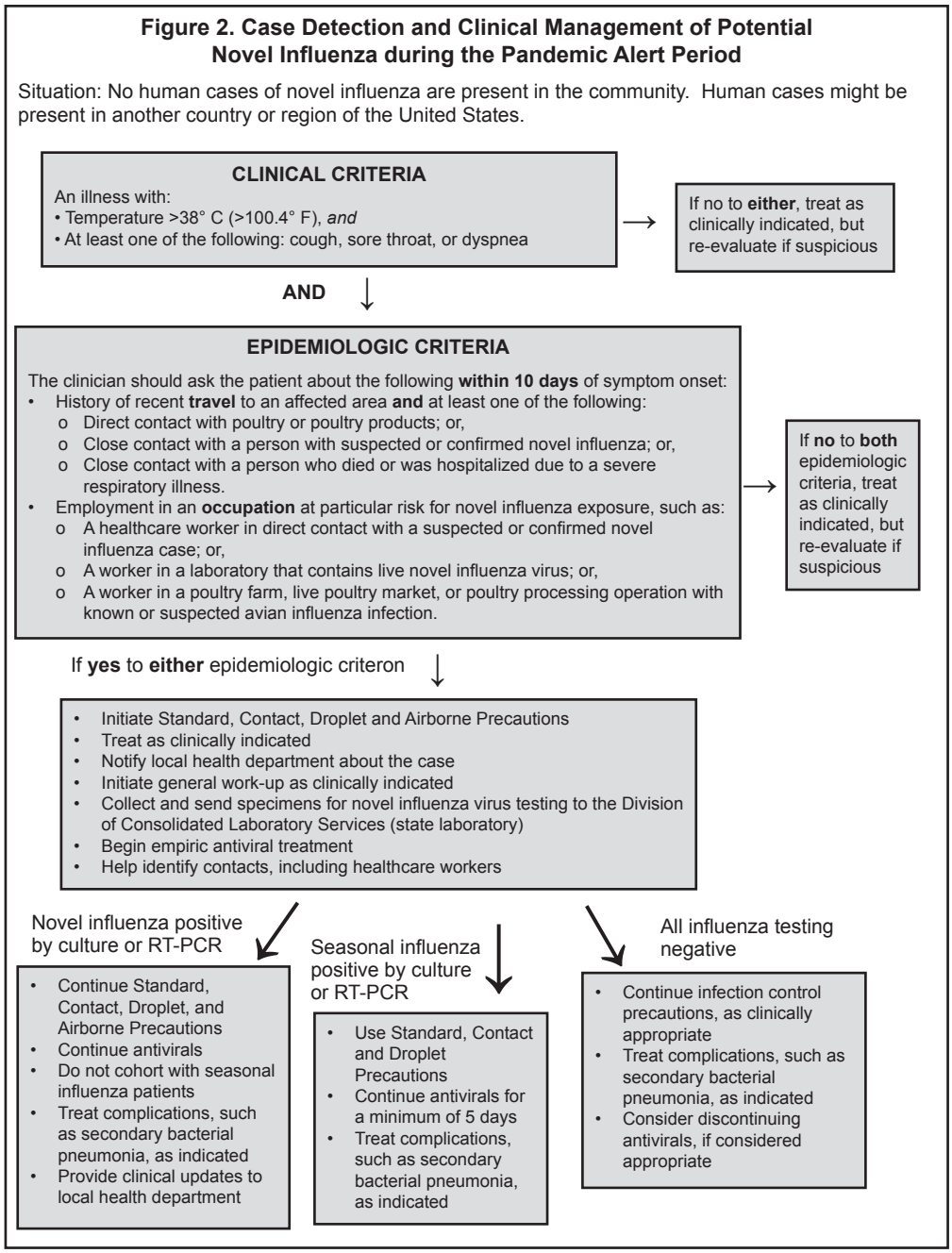
In addition to outbreak detection, Richmond and Norfolk are part of the "122 Cities Mortality Reporting System." This system reports to the CDC by week the number of deaths attributed to influenza and pneumonia.[8]

Immunization

Immunization is the major tool in the prevention of influenza. Unfortunately, several factors suggest that immunization may have a limited role in managing an influenza pandemic initially. These include:

- The particular strain of virus is unlikely to be identified until disease is already widespread, providing little forewarning for vaccine development;
- Only a single manufacturer produces influenza vaccine entirely within the U.S. Thus, even if existing U.S.-based influenza vaccine manufacturing capacity were completely diverted to producing a pandemic vaccine, supply would be severely limited; and,
- Annual influenza vaccine development typically requires 6-9 months before the vaccine is available in significant quantities since millions of fertilized hens' eggs must be available every day of production. At the same time, a pandemic influenza strain might be lethal to chickens, severely decreasing the available egg supply.[1]

Figure 2. Case Detection and Clinical Management of Potential Novel Influenza during the Pandemic Alert Period



As a result, supplies of vaccine will be scarce. Even after production starts, vaccine will be released in batches, and will have to be administered according to priority groups developed by the federal government. Adequate production for the entire population may take a year or more to accomplish under current manufacturing capabilities.[1]

In an effort to address these limitations, in May 2004 the U.S. awarded contracts to both Sanofi Pasteur and Chiron Corporation to manufacture an influenza A (H5N1) vaccine, using a vaccine candidate developed from isolates of the January 2004 avian influenza A (H5N1) from Vietnam. The Sanofi Pasteur vaccine started phase 1 trials for safety and immunogenicity in March 2005. The U.S. Department of Health and Human Services (DHHS) ordered two million doses of H5N1 vaccine in order to ensure that the manufacturing techniques, procedures, and conditions that would be used for large-scale production will yield a satisfactory product. While this vaccine could provide some protection if pandemic influenza does originate from the influenza A (H5N1) virus, it is unknown how well the vaccine produced to the 2004 influenza A (H5N1) virus would match the pandemic strain.[1]

Efforts are also being directed at developing cell culture manufacturing technology that can be applied to influenza vaccines. Using this technology, viruses are grown in bioreactors containing large number of cells in growth media, rather than eggs. The surge capacity afforded by cell-based technology can be adjusted to vaccine demand. Other techniques, such as methods to boost the immune response by changing the mode of delivery from intramuscular to intradermal, or the addition of immune-enhancing adjuvant to the vaccine formulation, are also being studied.[1]

Finally, given that post-influenza, bacterial, community-acquired pneumonia might affect approximately 10% of persons with pandemic influenza, efforts to maximize vaccination coverage against *Streptococcus pneumoniae* could be an important component of preparations. Current guidelines on the use of the 23-valent pneumococcal polysaccharide vaccine among adults and the 7-valent pneumococcal conjugate vaccine among children are available.[1]

Antiviral Medications

The second-line tools for the control of influenza are antiviral medications: the M2 inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). In general, antivirals are approved by the Food and Drug Administration (FDA) for use in two instances:

1. When treatment is started within 48 hours of symptom onset, these drugs decrease severity and duration of illness; and,
2. Primary prophylaxis for close contacts of infected individuals, individuals at increased risk of serious complications, or during a community outbreak. (Note: Vaccine is the drug of choice for prevention of influenza).[9]

However, concern exists over the impact of influenza virus resistance to these medications. Evidence suggests that avian influenza A (H5N1) has developed resistance to amantidine and rimantadine. This has shifted preparedness efforts to focus primarily on oseltamivir. Unfortunately, only a

single company (Hoffman-Roche in Basel, Switzerland) currently makes this drug, and the production process is complex and lengthy. As a result, there is limited ability to quickly acquire a large amount of the drug on demand.[1]

In response, antiviral medications are being added to the Strategic National Stockpile (SNS). As of October 2005, the SNS includes 2.3 million treatment courses of oseltamivir and 84,000 treatment courses of zanamivir. The SNS is expecting delivery on an additional two million courses of oseltamivir by the end of 2005. Similar to the vaccine, a priority list and guidelines for antiviral use has been developed by DHHS.[1]

Box 5 - DHHS Federal Influenza Plan Divisions[1]

Surveillance

Laboratory Diagnostics

Healthcare Planning

Infection Control

Clinical Guidelines

Vaccine Distribution and Use

Antiviral Drug Distribution and Use

Community Disease Control and Prevention

Managing Travel-Related Risks of Disease

Public Health Communications

Workforce Support: Psychosocial Considerations and Information Needs

While availability of stockpiles of antivirals and production of vaccine are primarily the responsibility of the federal government, the local distribution of preventive and therapeutic agents will be the responsibility of state and local health departments. As a result, VDH has been working to identify priority groups and developing estimates of resources needed to manage an influenza pandemic.

Containment

A third way to combat influenza infection is to reduce the potential for transmission between individuals and within the community. Influenza is easily and rapidly transmitted between humans and can spread through a community within a period of days to weeks. As a result, individual-based measures such as isolation and quarantine for influenza are very challenging, and they would only be effective at the early stages of a pandemic when there are a few localized cases. However, the Commonwealth has made significant progress in developing laws and procedures for the isolation and quarantine of individuals who may have a communicable disease of public health threat.

Slowing the spread of infection to allow time to develop and distribute vaccine and antivirals may require additional community-based measures. These could include a range of actions, such as short-term school or business closures, discouraging or banning large indoor gatherings such as sporting events and conventions, encouraging telecommuting, and discouraging travel in airplanes, buses, or mass transit. Personal protective equipment, such as masks, gowns, and gloves would be reserved for those working closely in the treatment of infected individuals, and would not be recommended for use by the general public.[1] In addition, VDH is designing training for all levels (public health, law enforcement, general public) related to community containment measures to maximize preparedness.

Pandemic Influenza Planning in Virginia

Virginia's Pandemic Influenza Response Plan was last revised in June 2005 (www.vdh.virginia.gov/epi/VaPanFluPlan_v062005_F.pdf). An Advisory Committee for Virginia Pandemic Influenza was formed in June 2005 and continues to meet regularly to revise influenza pandemic planning. The release of the DHHS National Pandemic Influenza Preparedness Plan in November 2005 (www.dhhs.gov/nvpo/pandemics/) has provided an important resource for further planning activities. As a result, VDH is working to incorporate elements of the national plan into state planning as quickly as possible. Key stakeholders from all levels will be involved in providing input into planning activities.

Conclusions

Although many infectious disease outbreaks (e.g. Severe Acute Respiratory Syndrome, viral hemorrhagic fevers) have the potential to cause widespread human infection, these infections are typically limited in their spread to either localized areas or regions, or to at-risk populations. Pandemic influenza, by contrast, is an explosive global event where most, if not all, populations worldwide are at risk for infection and illness. And while past pandemics have taken months or years to spread worldwide, modern travel patterns may lead to much more rapid dissemination. It is the sheer scope of influenza pandemics, with their potential to rapidly overwhelm societies and cause illnesses and deaths among all age groups, that distinguishes pandemic influenza from other emerging infectious disease threats. As a result, an influenza pandemic has the potential to cause more death and illness than any other public health threat.[1]

The timing, nature, and severity of the next influenza pandemic cannot be predicted with any certainty. The specific characteristics of a new pandemic influenza virus, such as virulence, transmissibility, initial geographic distribution, clinical manifestation, risk to different age groups and subpopulations, and drug susceptibility, will remain unknown until the pandemic begins. Minimizing social and economic disruption will require a coordinated response among governments, communities, and other public and private sector stakeholders.[1] Preparedness planning must also allow for flexibility and real-time decision-making that take new information into account as the situation unfolds.

The primary strategies for preventing pandemic influenza are the same as those for seasonal influenza: early detection, immunization, antiviral medications, and the use of infection control measures to prevent transmission. However, when a pandemic

begins, a vaccine may not yet be widely available, and the supply of antiviral drugs may be limited. The ability to reduce the impact will therefore rely heavily on healthcare professionals working closely with public health at all levels.[1] Preparation, including education and planning, ensures the best possible response to this emerging threat.

Box 6. For more information on avian and pandemic influenza, see the following:	
World Health Organization (WHO)	www.who.int/topics/influenza/en/
Centers for Disease Control and Prevention	www.pandemicflu.gov
Association of State and Territorial Health Officials (ASTHO)	www.astho.org
Infectious Disease Society of America	www.idsociety.org
National Foundation for Infectious Diseases	www.nfid.org
Institute of Medicine (IOM)	www.iom.edu
World Health Organization (WHO)	www.who.org

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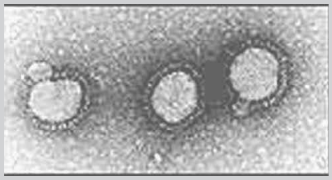
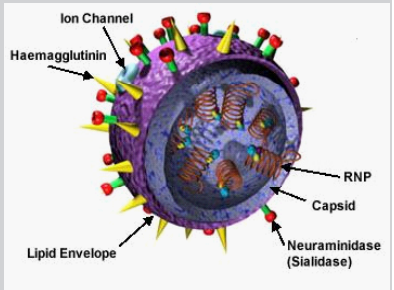
Flu Corner

Influenza Activity in Virginia and the U.S.

As of December 9, 2005, the Division of Consolidated Laboratory Services (DCLS) and hospital laboratories have reported one confirmed case of influenza A by direct fluorescent antibody (DFA). A commercial laboratory also reported one confirmed case of influenza A by DFA. As a result, Virginia influenza activity is listed as Sporadic (i.e., laboratory confirmed cases but no outbreaks of influenza-like illness detected; no increase in influenza-like illness). Overall, in the U.S. one state has reported local activity, 29 states have reported sporadic influenza activity, and 20 states have reported no activity. The proportion of deaths attributable to pneumonia and influenza in 122 cities monitored by the Centers for Disease Control and Prevention (CDC) was below the epidemic threshold.



The CDC reports that during the week ending December 3, 2005, 24 (1.3%) of 1,897 specimens tested by the World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories were positive for influenza. Since October 2, 2005, WHO and NREVSS laboratories have tested a total of 20,336 specimens for influenza viruses with 173 (0.9%) positives detected.



Of the 173 influenza isolates identified, 151 (87.3%) were influenza A viruses and 22 (12.7%) were influenza B viruses. Seventy-eight (51.7%) of the 151 influenza A viruses identified have been subtyped; 76 (97.4%) were H3N2 viruses and 2 (2.6%) were H1N1 viruses. The CDC has antigenically characterized 16 influenza viruses: 14 influenza A (H3N2) and two influenza B viruses. The influenza A (H3N2) viruses were characterized as A/California/07/2004-like [the influenza A (H3N2) component recommended for the 2005-06 influenza vaccine]. Influenza B viruses currently circulating can be divided into two antigenically distinct lineages represented by B/Yamagata/16/88 and B/Victoria/2/87 viruses. One of the influenza B viruses isolated belonged to the B/Yamagata lineage and was characterized as B/Florida/07/2004-like. This is a minor antigenic variant of B/Shanghai/361/2002, the recommended influenza B component for the 2005-06 influenza vaccine. The other influenza B virus was identified as belonging to the B/Victoria lineage.

Please see the CDC website at www.cdc.gov/flu/weekly/fluactivity.htm for up-to-date details on influenza surveillance in the U.S.

Public Health Activities

Multi-State Emergency Response Exercise

The VDH Emergency Preparedness and Response Programs conducted an emergency response exercise (OctoberTEST) from October 24-28, 2005. The exercise simulated both food-borne (botulism) and zoonotic (monkey pox) disease outbreaks, designed to test VDH's ability to respond to two emergencies, simultaneously, in different parts of the state.

As part of the exercise, VDH collaborated with West Virginia, North Carolina, Tennessee, and Kentucky. Thirteen local health districts in Virginia participated, as did 33 Virginia hospitals, the State Emergency Operations Center, and many state agencies, including: Agriculture and Consumer Services; Game and Inland Fisheries; Forestry; Environmental Quality; State Police; and Emergency Management. The Virginia National Guard was also involved. VDH is currently in the process of evaluating all aspects of the exercise to identify lessons learned.

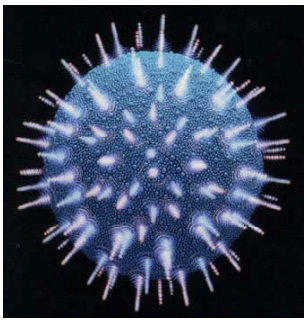
VDH Establishes Division of Disease Prevention

VDH has combined the former Division of HIV, STD and Pharmacy Services, and the former Division of Tuberculosis Control, into the new Division of Disease Prevention. This organizational change will allow VDH to integrate programs and capitalize on existing staff expertise through the establishment of new teams. This merger will also result in a leaner organizational structure modeled after the Centers for Disease Control and Prevention's (CDC) National Center for HIV, STD and TB Prevention. Casey Riley, formerly the Director of the Division of HIV, STD and Pharmacy Services, will be the director of the new division.

Syphilis Outbreak in Western Tidewater

Since mid-August, the VDH Division of Disease Prevention's Virginia Epidemiology Response Team (VERT) has assisted the Suffolk Health Department respond to an outbreak of syphilis. There were six reported cases of syphilis in Western Tidewater in 2004 and five from January–May 2005. An additional eight cases reported in June and July led to the decision to detail VERT to Suffolk in outbreak response mode in order to identify cases by the most rapid means available and enable interventions to begin before cases have a chance to spread the disease.

During a two-month deployment period, 19 more cases were diagnosed. Of these, 15 (79%) were identified via rapid case finding efforts that included case management, social networking, a media outreach campaign, and a community screening event.

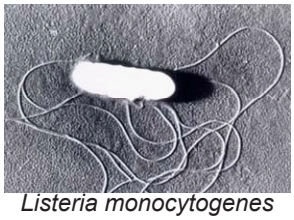


Created in 2000, VERT has assisted health departments across Virginia. In so doing, VERT has developed an operating plan that outlines three modes of action:

1. Assistance mode: a local health district requests personnel for a short period of time.
2. Assessment mode: when surveillance detects an increase or persistence of cases in a health district. Working with the local health department, an assessment is done to determine whether additional resources are needed.
3. Outbreak control: staff and resource deployment to address an outbreak.

Listeria Investigation

Platelets collected from two donors at a Red Cross blood donation center in Virginia have tested positive for *Listeria*, a microorganism that can cause meningoencephalitis and septicemia. Investigators from the Roanoke Health District, VDH Office of Epidemiology, and the CDC have conducted an investigation as to how the platelets may have become contaminated. The platelets have been destroyed and none were distributed to hospitals for patient use.



Listeria monocytogenes

VDH Division of Disease Prevention Expands HIV Incidence and Resistance Testing Programs

VDH is one of 34 grantees funded by the CDC to implement HIV incidence and resistance testing. Incidence testing measures at a population-level how many individuals were newly infected with HIV in the last year. Resistance testing determines the prevalence and transmission of drug-resistant viruses and other atypical viruses. Ultimately, incidence and resistance data enable the Division to better target HIV prevention and education efforts and allow public health authorities to make improved treatment recommendations for HIV-infected Virginians.

Between June 2004 and May 2005, the Virginia Incidence/Resistance (I/R) Programs were successfully piloted and implemented in the public STD clinics of Arlington, Norfolk, and Richmond City. The Division received extensive support from these pilot sites and has utilized the lessons learned there to facilitate statewide expansion. Beginning in the summer of 2005, program expansion was undertaken for the remaining state public health departments. To date, 16 health districts are collecting I/R data.

In September, 2005, the I/R Coordinator and the southwest region's Program Consultant introduced the programs to the Danville/Pittsylvania, New River, Cumberland Plateau, Lenowisco, Mount Rogers, Roanoke, Alleghany and West Piedmont Health Districts. The goal will be to expand the two programs statewide by the end of 2005.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, October 2005						Total Cases Reported Statewide, January - October		
		Regions							
	State	NW	N	SW	C	E	This Year	Last Year	5 Yr Avg
AIDS	85	2	33	3	5	42	516	562	609
Campylobacteriosis	67	11	20	9	9	18	506	560	544
***E. coli* O157:H7**	11	1	7	1	2	0	40	33	47
Giardiasis	57	18	9	15	8	7	469	440	332
Gonorrhea	599	36	45	77	197	244	7,017	7,403	8,318
Hepatitis, Viral									
A	10	1	4	1	2	2	71	108	111
B, acute	8	2	0	2	0	4	126	214	162
C, acute	1	1	0	0	0	0	11	16	7
HIV Infection	62	4	12	8	8	30	658	714	705
Lead in Children†	55	4	5	13	20	13	531	687	649
Legionellosis	4	0	0	1	0	3	37	41	39
Lyme Disease	42	5	24	3	2	8	209	150	122
Measles	0	0	0	0	0	0	0	0	<1
Meningococcal Infection	6	1	0	3	0	2	29	18	30
Mumps	0	0	0	0	0	0	0	9	6
Pertussis	24	2	9	4	1	8	302	170	103
Rabies in Animals	47	11	4	14	12	6	410	425	458
Rocky Mountain Spotted Fever	22	0	4	3	3	12	95	29	24
Rubella	0	0	0	0	0	0	0	0	0
Salmonellosis	102	14	22	15	19	32	971	1,004	979
Shigellosis	11	2	7	2	0	0	110	136	403
Syphilis, Early§	30	0	10	0	3	17	238	173	180
Tuberculosis	42	2	19	2	8	11	245	225	222

Localities Reporting Animal Rabies This Month: Albemarle 1 cow; Amherst 1 skunk; Arlington 1 raccoon; Brunswick 1 fox; Campbell 1 cat, 1 skunk; Carroll 1 skunk; Charles City 1 fox; Chesapeake 1 raccoon; Chesterfield 2 bats; Fauquier 2 raccoons, 1 skunk; Gloucester 1 skunk; Goochland 2 raccoons, 1 skunk; Grayson 1 raccoon, 1 skunk; King and Queen 1 skunk; Loudoun 1 raccoon; Lunenburg 2 skunks; Montgomery 1 bat; New Kent 1 skunk; Northampton 1 raccoon; Nottoway 1 fox; Page 1 skunk; Patrick 2 skunks; Prince William 2 raccoons; Pulaski 2 skunks; Shenandoah 1 cat, 1 fox; Spotsylvania 1 raccoon; Stafford 2 skunks; Sussex 1 skunk; Virginia Beach 1 bat; Waynesboro 1 raccoon; Wythe 1 cat, 1 raccoon, 1 skunk; York 1 raccoon.

Toxic Substance-related Illnesses: Adult Lead Exposure 23; Asbestosis 1; Mercury Exposure 4; Methemoglobin 1; Pneumoconiosis 3.

*Data for 2005 are provisional. †Elevated blood lead levels ≥10µg/dL. §Includes primary, secondary, and early latent.

Public Health Award

2005 Commissioner's Award for Distinguished Public Health Service: Dr. Suzanne Jenkins

State Health Commissioner Robert B. Stroube, M.D., M.P.H., recently announced the creation of a new award, "The State Health Commissioner's Award for Distinguished Public Health Service." The award will be given annually to a Virginia Department of Health employee 1) whose contributions have been beyond the call of duty in achieving the goals and ideals of public health; 2) who has effectively applied advocacy skills, scientific knowledge or innovative organizational efforts to advance public health; 3) who has overcome hurdles to generate support for one or more organizational objectives; and 4) whose achievements can be leveraged by others. The recipient may have contributed in any field of public health practice, (e.g., technical service, administration, education, or research).

The 2005 recipient of the award is Suzanne Jenkins, V.M.D., M.P.H. (Office of Epidemiology). Dr. Jenkins was selected based on the following personal and professional attributes:

- The extent to which her integrity and advice are respected in Virginia and nationally;
- Her ability to take scientific findings and communicate them effectively to any audience;
- Her reputation as a public health professional whom the public, media, state legislators, and her professional peers all trust; and
- Her skill at distilling research and utilizing it to help establish balanced public health policy.