

H5N1 Influenza - A New Threat

Influenza virus has been classified into three types based on nucleocapsid protein: influenza A, B, and C. Humans can be infected by all types of influenza, although type C results causes only mild infection and is not associated with epidemics. All influenza viruses undergo frequent point mutations resulting in continuous antigenic changes known as antigenic drift. This allows the virus to evade immunity, although prior exposure to the same subtype provides partial immunity. An epidemic may occur with antigenic drift. Because of antigenic drift, a new influenza vaccine (currently composed of two A subtypes and one B type) is made yearly to protect against seasonal influenza.

Influenza A virus is classified by subtype incorporating the type of hemagglutinin (abbreviated as H) and neuraminidase (abbreviated as N). H and N are viral surface antigens. Antigenic shift is the exchange of a gene segment resulting in a new subtype (re-assortment), or an adaptive mutation resulting in a major antigenic change. Re-assortment occurs if two different influenza A viruses re-assort with each other when there is dual infection in the same host. Influenza viruses are host-specific; however, pigs can be infected by avian and human strains of influenza A and re-assortment from avian and human strains co-infecting a pig can occur. Adaptive mutation occurs over time in the same virus and is thought to have happened with the 1918 strain of influenza that was originally an avian strain, but adapted to become readily transmissible in humans. Because antigenic shift results in a novel virus, there is no

prior immunity and a pandemic (i.e., worldwide epidemic) can result such as occurred in 1918, 1957, and 1968.

Birds of all species are thought to be susceptible to avian strains of influenza A. A low pathogenic virus is manifested in birds by ruffled feathers and decreased egg production. A high pathogenic virus is extremely contagious and rapidly fatal.

Transmission of avian influenza A to humans resulting in human infection has been documented a number of times. In 1997, 18 human cases of H5N1 avian influenza in Hong Kong were reported. Six people died and three were severely ill. The source of the outbreak was infected chickens and the outbreak was contained when all the chickens were culled in the affected region.

The current H5N1 outbreak came to attention in December 2003, when deaths in poultry in Korea were reported. On January 11, 2004 Vietnam reported that H5N1 influenza was identified as the agent causing human cases of severe respiratory disease. Subsequently, H5N1 has been reported in birds from countries in Asia, Africa and Europe. As of March 24, 2006, a total of 186 human cases and 105 deaths have been reported in eight countries including Vietnam (93 cases), Indonesia (29 cases), Thailand (22 cases), China (16 cases), Turkey (12 cases), Azerbaijan (7 cases), Cambodia (5 cases), and Iraq (2 cases).

Most H5N1 patients have had a history of direct contact with poultry. There is evidence of human-to-human trans-

mission in some small clusters, including a case of a child-to-mother transmission where there was prolonged unprotected exposure to the child's respiratory secretions.¹

Most patients have been previously healthy and presented with respiratory symptoms. Typically, fever and lower respiratory symptoms are present. Watery diarrhea may precede respiratory symptoms. Vomiting, pleuritic pain, and bleeding from the gums and nose may occur. Lower respiratory manifestations are usually present at the time of seeking clinical care. Chest radiographs generally depict abnormalities including diffuse, multifocal, patchy or interstitial infiltrates or segmental or lobar consolidations with air

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bronchograms.² Atypical presentations have included diarrhea and encephalitis.³ The frequencies of milder illnesses and subclinical infections are unknown. Lower respiratory disease may progress to the acute respiratory distress syndrome. Multi-organ failure may occur. Common laboratory findings have included lymphopenia and thrombocytopenia.²

Sequencing of H5N1 indicates resistance to amantadine and rimantadine. Early initiation of oseltamivir appears to be beneficial, although a couple of fatal cases have been reported that had H5N1 which was resistant to oseltamivir.⁴ Mouse data indicate a higher dose and longer duration of oseltamivir may be needed to treat infection with the current strain of H5N1.⁵ Treatment recommendations for H5N1 are evolving and more data are urgently needed. The World Health Organization (WHO) Writing Committee recommends a standard dose (75 mg bid for 5 days in adults) for early, mild cases, and consideration of doubling the dose of oseltamivir and extending it for 7-10 days in cases of severe infection.² However, the WHO in a March 17, 2006 bulletin said that there is no clear evidence that higher doses of oseltamivir will be more effective for patients with H5N1. At this point, standard doses are recommended, although there is an acknowledgement in the bulletin that severely ill patients may benefit from a longer duration and higher dose of oseltamivir. In terms of safety, a 300 mg/day dose is generally well tolerated, although gastrointestinal side effects may increase with higher doses, especially those >300 mg/day. MDH will provide updated information on dosing, when available, on the MDH website at www.health.state.mn.us If you are treating a case of H5N1, consultation with an infectious disease expert is recommended.

WHO has classified the phases of a pandemic due to influenza. The interpandemic period contains phases 1 and 2. Phase 1 occurs when no new influenza virus subtypes have been detected in humans. Phase 2 occurs when no new influenza virus subtypes have been detected in humans; however, a circulating animal influenza virus subtype poses a substantial risk of

human disease. The pandemic alert period contains phases 3 and 4. Phase 3 occurs when there are human infections with a new subtype but no human-to-human spread or rare instances of spread to a close contact occurs. Phase 4 occurs when small clusters with limited human-to-human transmission are observed but spread is highly localized, suggesting that the virus is not well adapted to humans. Phase 5 occurs when larger clusters of human transmission are seen 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). Phase 6 is the pandemic phase with increased and sustained transmission in the general population. Following this is the post-pandemic period and then the return to the interpandemic period (Phase 1).

At this point in time (Phase 3 – pandemic alert period), clinicians should question patients being clinically evaluated for possible H5N1 influenza about their potential exposure to H5N1. A suggested clinical evaluation to potential cases of H5N1 during the pandemic alert period is outlined on page 11. The Minnesota Department of Health (MDH) should be called (24/7) at 651-201-5414 or 1-877-676-5414 if there is a patient in which you suspect H5N1. Laboratory testing at MDH may be indicated.

There is great concern among public health professionals that because of the widespread occurrence of H5N1 in birds, that there is a substantial risk of H5N1 avian influenza virus evolving into a pandemic strain. A pandemic would result in high morbidity, mortality, overload the healthcare system and cause a major disruption in society. In 1918, it is estimated that 20% of the world's population was infected with influenza resulting in 40 million deaths. The highest morbidity was in those aged 20-40 years. Tremendous efforts are going into planning for a potential pandemic on many levels including vaccine research, stockpiling supplies including antivirals, planning for healthcare surge capacity, planning for social distancing measures, and planning for essential personnel in all aspects of society.

In Minnesota, MDH estimates (based on a U.S. Centers for Disease Control and Prevention formula derived from prior pandemics) that a pandemic would result in 1,544,000 ill, with 772,000 patients requiring outpatient medical care, 15,000 - 172,000 patients hospitalized, 2,250 – 25,700 requiring intensive care (including 1,120 – 12,900 requiring mechanical ventilation), and 3,600 – 32,900 deaths from influenza. It is thought that a pandemic would occur in waves, with the first wave lasting 6-8 weeks. These are estimates and much will depend on the virulence of the virus, the transmissibility of the virus and the effectiveness of prevention and control methods.

MDH is working on a "living plan", which will be adapted depending on the specific characteristics of the viral strain and the pandemic. The clinical approach to patients will be adapted depending on the epidemiology, clinical manifestations, virus susceptibility, and available resources. The plan and updates to the plan will be posted on the MDH website at:

www.health.state.mn.us. Please check the MDH website frequently for updates.

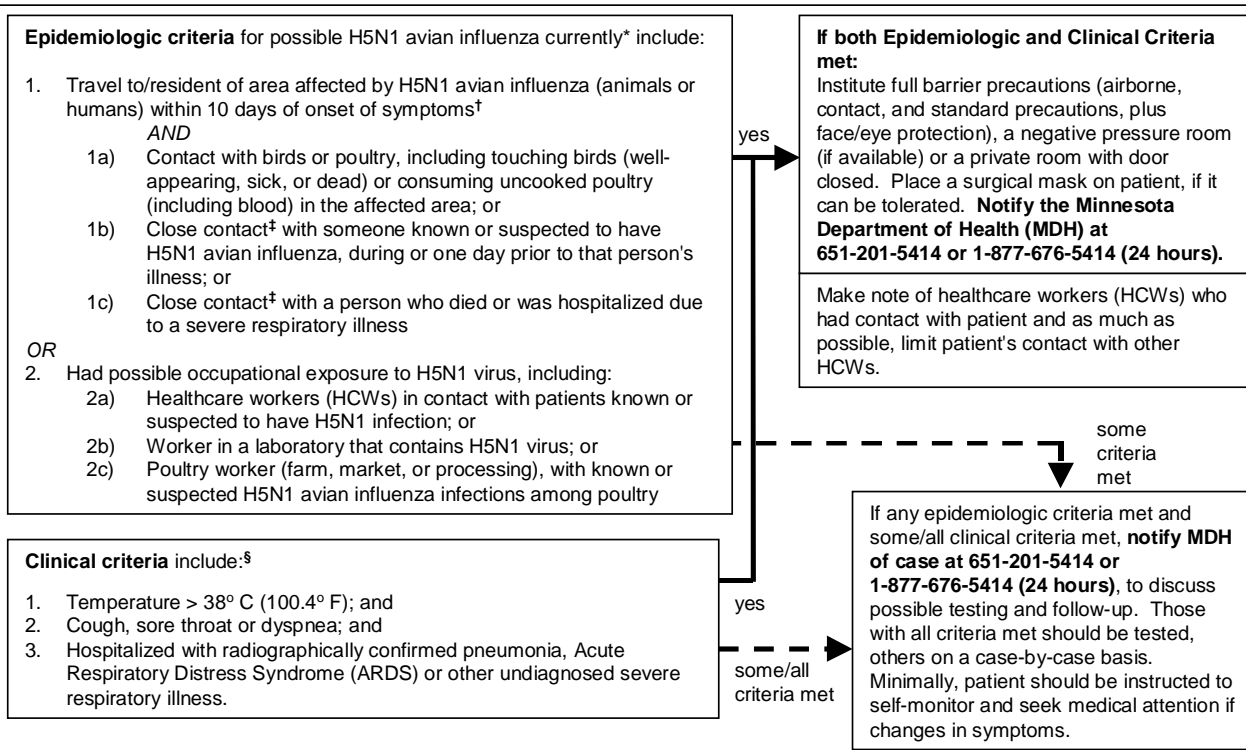
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Recommended Clinical Evaluation for Possible H5N1 Influenza During Pandemic Alert Period (3/2006)

Pandemic Alert (pre-pandemic)

- No human cases of H5N1 avian influenza infection occurring in community.
- Human cases may be present elsewhere in world or other region of U.S. but no pandemic declared and no widespread human-to-human transmission.
- Goals of clinical evaluation in this period are to identify possible cases of H5N1 influenza, establish that diagnosis or an alternate etiology.
- *First, question patients with influenza-like illness (ILI) about travel in past 10 days, and occupation.*



Initiate Clinical Evaluation (should be guided by clinical presentation):[¶]

Use full barrier precautions (airborne, contact, and standard precautions, plus face/eye protection) and place patient in a negative pressure room, if possible, when obtaining respiratory specimens. Consider use of a positive air purifying respirator (PAPR) for procedures that may generate aerosols.

1. Pulse oximetry, chest radiograph, complete blood count with differential, blood cultures, serum chemistries, as indicated. Serum for acute serology (convalescent serology after 3 weeks).
2. Testing at MDH: Collect specimens for PCR testing for H5N1 virus. For swabs, use a dacron or rayon swab with a plastic or aluminum shaft. Store in viral transport media and hold at 4° C (39° F) until transport to MDH Laboratory can be arranged (MDH epidemiologist will assist in arranging transport). Specimens will be used for H5N1 evaluation and for evaluation of other respiratory pathogens by PCR at MDH (including adenovirus, influenza B, parainfluenza, RSV, human metapneumovirus, *Legionella* spp., *M. pneumoniae*, and *C. pneumoniae*). Other specimens may be requested depending on clinical features. **Do not attempt to perform viral culture. Culture for H5N1 should only be done at a BSL3+ or BSL4 facility.**
3. Sputum culture and gram stain (and/or tracheal aspirate, if intubated, pleural effusion aspirate, if present). Antimicrobial susceptibility testing for bacterial isolates.
4. In adults with radiologically confirmed pneumonia, consider urine antigen testing for *Legionella* and *S. pneumoniae*.

Treatment, contact tracing and ongoing monitoring:

1. Clinical treatment including antibacterial agents and antiviral agents (neuraminidase inhibitors) as indicated. Antivirals should be started as soon as possible (most efficacious if used within 48 hours). Note: antiviral recommendations are evolving. Standard adult treatment dose of oseltamivir is 75 mg bid x 5 days. See product information for pediatric dosing. Some clinicians recommend a higher dose and duration of oseltamivir for seriously ill patients (150 mg bid x 7-10 days for adults). Consultation with ID clinician recommended.
2. Complete H5N1 Avian Influenza Screening Form (MDH website: www.health.state.mn.us), including any initial information on contacts of the patient, from one day before the case's onset of illness to the present.
3. MDH will provide assistance with diagnostic evaluation and results, isolation/quarantine issues, and case status.

Footnotes

- * Changes in epidemiologic criteria or clinical evaluation recommendations will be posted at: <http://www.cdc.gov/flu/avian/index.htm> and <http://www.health.state.mn.us>.
- † The latest information on the geographic locations of H5N1 in humans can be found at the World Health Organization (WHO) website: https://www.who.int/csr/disease/avian_influenza/country/en/index.html and geographic locations of H5N1 in animals can be found at the World Organization for Animal Health (OIE) website: http://www.oie.int/download/AVIAN%20INFLUENZA/A_Al-Asia.htm.
- ‡ Close contact is defined as having cared for or lived with a person known to have avian influenza or having a high likelihood of direct contact with respiratory secretions and/or body fluids of such a person.
- § Typical symptoms are respiratory; however, note that some cases have presented with encephalitis or diarrhea.
- ¶ Rapid influenza assay results should be viewed with caution. The sensitivity and specificity of these assays are not known for H5N1.
- || H5N1 may be more easily detected from a throat swab.

Minnesota Department of Health Infection Control Recommendations for Avian and Pandemic Influenza

Figure 1. Minnesota Department of Health Infection Control Recommendations for Avian and Pandemic Influenza

The Minnesota Department of Health recommends airborne* and contact precautions, plus eye protection, in addition to standard precautions (“full barrier precautions”) for all known and suspect avian and pandemic influenza patients.

Personal protective equipment (PPE) for full barrier precautions,[†] includes:

- respirator at least as protective as a NIOSH-certified N95 respirator;[‡]
- gown;
- gloves; and
- eye protection (faceshield/goggles)

In making these recommendations, MDH acknowledges that supplies of PPE necessary to implement full barrier precautions, particularly respirators, may be limited during a pandemic. The Institute of Medicine is currently formulating recommendations for the reuse of disposable particulate respirators. MDH will provide guidance on prioritization and possible reuse of PPE when supplies are limited.

*Airborne precautions include patient placement in a airborne infection isolation room, if available. To access more information about this topic, see www.cdc.gov/ncidod/dhqp/gl_environinfection.html

[†]Full barrier PPE posters are available on the MDH website at: www.health.state.mn.us/divs/idepc/dtopics/infectioncontrol/ppe/

[‡]Respirators should be used in the context of a complete respiratory protection program as required by OSHA. This includes training, fit-testing, and fit-checking to ensure appropriate respirator selection and use. To be effective, respirators must seal properly to the wearer’s face. Detailed information on respiratory protection programs is available at: www.osha.gov/SLTC/etools/respiratory/ and www.health.state.mn.us/divs/idepc/dtopics/infectioncontrol/rpp/index.html

The following are summaries of current U.S. infection control recommendations for avian and pandemic influenza, and relevant website addresses.

U. S. Centers for Disease Control and Prevention (CDC)

For avian influenza, the current CDC guidance recommends airborne and contact precautions, plus eye protection, in addition to standard precautions. It is noted on the CDC website that this guidance is under revision and will be re-posted when final. This guidance can be accessed at: www.cdc.gov/flu/avian/professional/infect-control.htm

U. S. Occupational Safety and Health Administration (OSHA)

For avian influenza, OSHA recommends airborne and contact precautions, plus eye protection, in addition to standard precautions. This guidance can be accessed at: www.osha.gov/dsg/guidance/avian-flu.html

U. S. Health and Human Services (HHS)

For pandemic influenza, the HHS Pandemic Influenza Plan recommends

droplet precautions (use of surgical or procedure mask when within 3 feet of patient), in addition to standard precautions. This guidance can be accessed at: www.hhs.gov/pandemicflu/plan/sup4.html#modes

However, for pandemic influenza, airborne and contact precautions, plus eye protection are recommended for:

- aerosol-generating procedures;
- pandemic influenza exhibiting increased transmissibility;
- the initial stages of an outbreak of an emerging or novel strain of influenza; and
- as determined by other factors such as vaccination/immune status of personnel and availability of antivirals.

Minnesota Department of Health (MDH) Recommendations

MDH recommends full barrier precautions: airborne and contact precautions, plus eye protection, in addition to standard precautions for all known and suspect cases of H5N1 avian influenza or pandemic influenza (Figure 1). The rationale for these recommendations is based upon an understanding of respiratory aerosols and their transmis-

sion, and the recognition that one of the possible modes of transmission of influenza is the airborne route. These concepts are reviewed below.

Respiratory Aerosols

Infectious respiratory aerosols of varying sizes are generated when an individual coughs, sneezes or talks.¹ A cough can contain up to 100,000 particles and a sneeze can generate 20 times more particles than a cough.² The greater the force and pressure involved in aerosol generation, the smaller the expelled particles will be. The smallest particles evaporate quickly and the dried residues that remain (droplet nuclei), are so small that they can be carried on air currents a considerable distance from the source and remain suspended in the air for substantial lengths of time and infect people at some distance from the source.¹ Particle size determines where particles are deposited in the respiratory tract of the host. Where the particles are deposited can determine whether or not infection will occur; e.g., smaller particles may be deposited lower in the respiratory tract than larger particles.³

Infectious particles are generally measured in microns (one inch is equivalent to 25,400 microns [mm]). CDC infection control guidelines cite a particle size of 5 mm as a break point that distinguishes between diseases spread by “droplet transmission” (particles \geq 5 mm) and diseases spread by “airborne transmission” (particles < 5 mm).⁴ Larger droplets are thought to typically travel no more than 3 feet while small particle aerosols have the ability to travel longer distances. Larger droplets are thought to be deposited mainly in the mucous membranes of the nose, eyes, and mouth; small particle aerosols are more likely to be deposited in the lower respiratory tract.

Communicable diseases are classified by their presumed route of transmission (e.g., droplet, contact, or airborne) and infection control recommendations are based on this classification. Current CDC guidelines recommend that healthcare workers wear a surgical mask when working within 3 feet of patients with an infection spread via the droplet route, and a respirator when in the same room as a patient with an infection spread via the airborne route.

However, transmission of respiratory particles is quite complex. In reality, there is not a clear delineation between droplet and airborne transmission, and the distances that particles travel can vary (e.g., particles \geq 5 mm can travel more than three feet).⁵ In addition, the length of time particles remain airborne varies and is determined by particle size, settling velocity, and airflow in the area. Also there is not a predictable size for droplet nuclei; final size depends on the nature of the fluid that contained the organism, the initial size of the aerosol, environmental conditions (e.g., temperature, relative humidity, airflow), the time spent airborne, and the size of the organism within a droplet.

Human Influenza Transmission

Using current CDC infection control terminology, there is evidence that influenza is transmitted between humans via small particle aerosols (airborne transmission), larger droplets (droplet transmission), as well as by direct and indirect contact (contact transmission)^{3, 4, 6, 7} The relative

importance of each route of transmission is unclear.

Evidence for Airborne Transmission of Influenza

The explosive spread of influenza after introduction into a community has long suggested the possibility of airborne transmission. There are several reports in the literature describing observational evidence of airborne transmission of influenza in humans. Tuberculosis patients housed in a building with ceiling ultraviolet radiation (which is known inactivate influenza virus and to reduce airborne disease transmission)⁸ during the 1957-58 pandemic were less likely to become infected with influenza than tuberculosis patients housed in a building without ultraviolet radiation.⁹ In 1979, aircraft passengers, including a passenger who became acutely ill with influenza within 15 minutes of boarding the plane, were detained on a runway for 4.5 hours during which time the ventilation system was turned off for 2-3 hours. The ill passenger stayed on the plane the entire time and the other passengers and crew were free to come and go. Within 72 hours, 72% of the passengers and crew subsequently developed influenza-like-illness (91% with confirmed influenza). The risk of illness was dependent on the amount of time spent on board.¹⁰

Other published reports have provided experimental evidence of airborne transmission of influenza in humans. The infectious dose of influenza is 10-100 fold lower when small particle aerosols are delivered to the lower respiratory tract (mimicking airborne transmission), rather than when delivered as intranasal drops (mimicking droplet transmission).¹¹ In addition, influenza virus administered intranasally typically does not cause cough or lower respiratory tract symptoms, whereas early onset of cough and protracted cough are associated with natural influenza infection.¹² Two recent articles have demonstrated that H5N1 preferentially binds to cells of the lower respiratory tract rather than the upper respiratory tract. This finding may explain the relatively rare amount of person-to-person transmission seen to date.^{13,14}

Experimental evidence of airborne transmission of influenza in animals has been provided in several published studies. In one study, infected and

uninfected mice were placed in a closed chamber in which the airflow could be manipulated. As the rate of airflow increased, the rate of influenza transmission decreased proportionately. In a setting of constant airflow, one group of uninfected mice were separated from infected mice by a screen while another group of uninfected mice were on the same side of the screen as the infected mice. The infection rates in both groups of initially uninfected mice were similar.¹⁵ In another study, uninfected mice placed in an unventilated room with constantly agitated air and low relative humidity, became infected with influenza as late as 24 hours after virus was aerosolized into the room. As relative humidity levels were increased, the virus was infective for shorter periods of time. The possibility of re-aerosolization of influenza virus is supported by increased infectivity of the air after the floor of the room was vigorously swept.¹⁶ Another study found that a highly transmissible influenza strain could be recovered easily from the air surrounding infected mice during the period when they were most infectious, but there was no recoverable virus in the air surrounding mice infected with a less transmissible influenza strain during the same period.¹⁷ Finally, efficient transmission of influenza from infected to uninfected ferrets was demonstrated whether or not the ferrets were separated by a long straight air duct or by air ducts in the shape of an “s” or a “u.”¹⁸

Influenza Transmission in Healthcare Facilities

Unfortunately, the data on influenza transmission in health care facilities are very limited and it is not possible to determine all the modes of potential transmission. Available data are often cited as indicating that droplet transmission is the primary mode of transmission in healthcare facilities; however, other modes cannot be ruled out. During the 1957-58 influenza pandemic, an acutely ill patient was admitted to a four-person hospital room with no precautions. Subsequently, roommates, health care workers, and other ward patients became ill. The epidemic curve suggested a point source outbreak with additional droplet or contact spread, rather than a single source outbreak, which would be more likely to be associated with airborne transmission...
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mission.¹⁹ More recent influenza experiences at two U.S. hospitals have also been reported. In one hospital, transmission of influenza was rarely noted; most rooms were private, but had positive pressure.³ In the other hospital, transmission of influenza in pediatric patients was most often observed among patients in the same room, particularly those in adjacent cribs. Patients in other rooms in the same ward were less likely to become infected, even though room doors were open and influenza patients were not housed in negative pressure rooms.⁶ It should be noted in interpreting the latter study, that pediatric patients do not typically have a forceful cough and are known to be less likely to transmit airborne diseases such as tuberculosis.²⁰ Clearly, additional data would be helpful in determining the relative importance of the different modes of transmission of influenza in various settings including healthcare facilities.

Respiratory Protection

It is important to understand how respiratory protection equipment works. Respirators are designed to protect the wearer from respiratory aerosols expelled by others. Surgical masks are designed to protect the sterile field from respiratory aerosols expelled by the wearer and are not designed to offer respiratory protection to the wearer. Although there are no data on the efficacy of respirators vs. surgical or procedure masks in preventing transmission of influenza to health care workers, there are data demonstrating the poor filtration and fit capacity of single or even multiple surgical masks worn at one time.²¹⁻²⁴ In addition, surgical and procedure masks are not evaluated for fit and cannot be properly fitted to the face or tested for fit and do not prevent leakage around the edge of the mask when the user inhales. It is important to note that there are no minimum standards for surgical or procedure mask filter efficiency, there are a wide variety of filter efficiencies among available masks, and most masks do not effectively filter small particles from the air.

Conclusions

- Influenza may be transmitted by small particle aerosols and surgical masks do not offer adequate protection against the inhalation of these particles.

- To minimize exposure of healthcare workers to avian and pandemic influenza virus, MDH recommends that healthcare workers use full barrier precautions, including respirators (if available*), when working with known or suspect avian or pandemic influenza patients.
- Providing appropriate protection to healthcare workers during a pandemic is critical because:
 - vaccine for the pandemic influenza strain is unlikely to be available in the initial stages of a pandemic;
 - antiviral supplies are likely to be limited; and
 - pandemic influenza may cause disproportionate morbidity and mortality in younger, healthier people, such as healthcare workers, as it did in the 1918 pandemic.

*If respirators are unavailable, use a tight fitting surgical mask

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Expansion of the Range of Vector-borne Disease in Minnesota

In recent years, the Minnesota Department of Health (MDH) has documented an expansion of the areas in which Minnesota residents are exposed to several vector-borne diseases. This expansion may be due to changes in human behavior, vector or pathogen distribution, and/or vector density and infection rates.

As part of the follow-up on reported cases of mosquito- and tick-transmitted disease, MDH staff contacted case-patients to ascertain likely areas of exposure to vector species. Then, during the summer of 2005, MDH staff began an effort to clarify the distribution areas in Minnesota of two vector species:

Ixodes scapularis (deer tick or black-legged tick, the vector of Lyme disease, human anaplasmosis, and babesiosis) and *Ochlerotatus triseriatus* (Eastern Tree Hole mosquito, the vector of La Crosse encephalitis). This article reports on those findings.

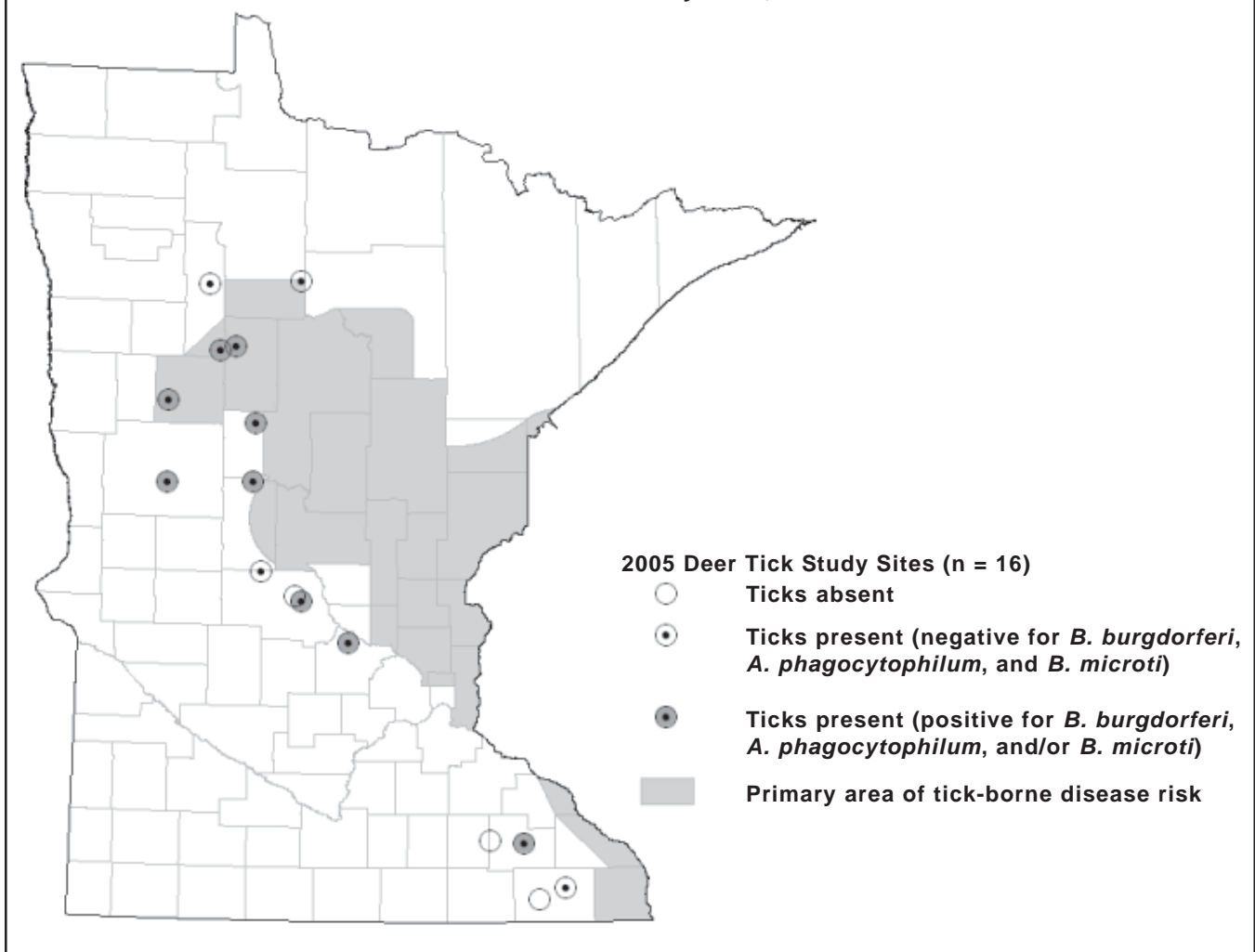
Tick-borne Disease

Pathogens transmitted by *I. scapularis* ticks in Minnesota include *Borrelia burgdorferi* (Lyme disease agent), *Anaplasma phagocytophilum* (human anaplasmosis agent), and *Babesia microti* (babesiosis agent). Most tick-borne disease case-patients in Minnesota historically have been exposed to infected ticks in forested portions of east

central counties or in the Saint Croix and Mississippi River valleys of eastern and southeastern Minnesota. Recent data, however, suggest that exposures are occurring in areas of northern, west central, central, and southeastern counties on the periphery of the historical endemic range, indicating a northward and westward expansion of disease risk. A recent *Disease Control Newsletter* article elaborated on these trends in human disease incidence and exposure. (See "Dramatic Increase in Lyme Disease and Other Tick-borne Diseases, 2004" in the May/June 2005 issue [vol. 33, no. 3].)

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Figure 1. Areas of Highest Risk for Tick-borne Disease in Minnesota, and Minnesota Department of Health Deer Tick Study Sites, 2005



The expanding tick-borne disease risk in Minnesota may be associated with the recent establishment of disease-carrying tick populations in new areas of the state. Despite the lack of systematically collected historical data on tick abundance in these areas, anecdotal reports from land managers, residents, and visitors support this hypothesis. Also, MDH has noted an increasing number of case-patients in new areas.

The deer tick distribution study implemented by MDH in the summer of 2005 had two components: 1) field sampling in emerging areas of the state to confirm and compare tick presence and abundance; and 2) polymerase chain reaction (PCR) testing of these ticks for tick-borne disease agents. MDH field staff surveyed 16 forested sites at the edge of Minnesota's known tick-borne dis-

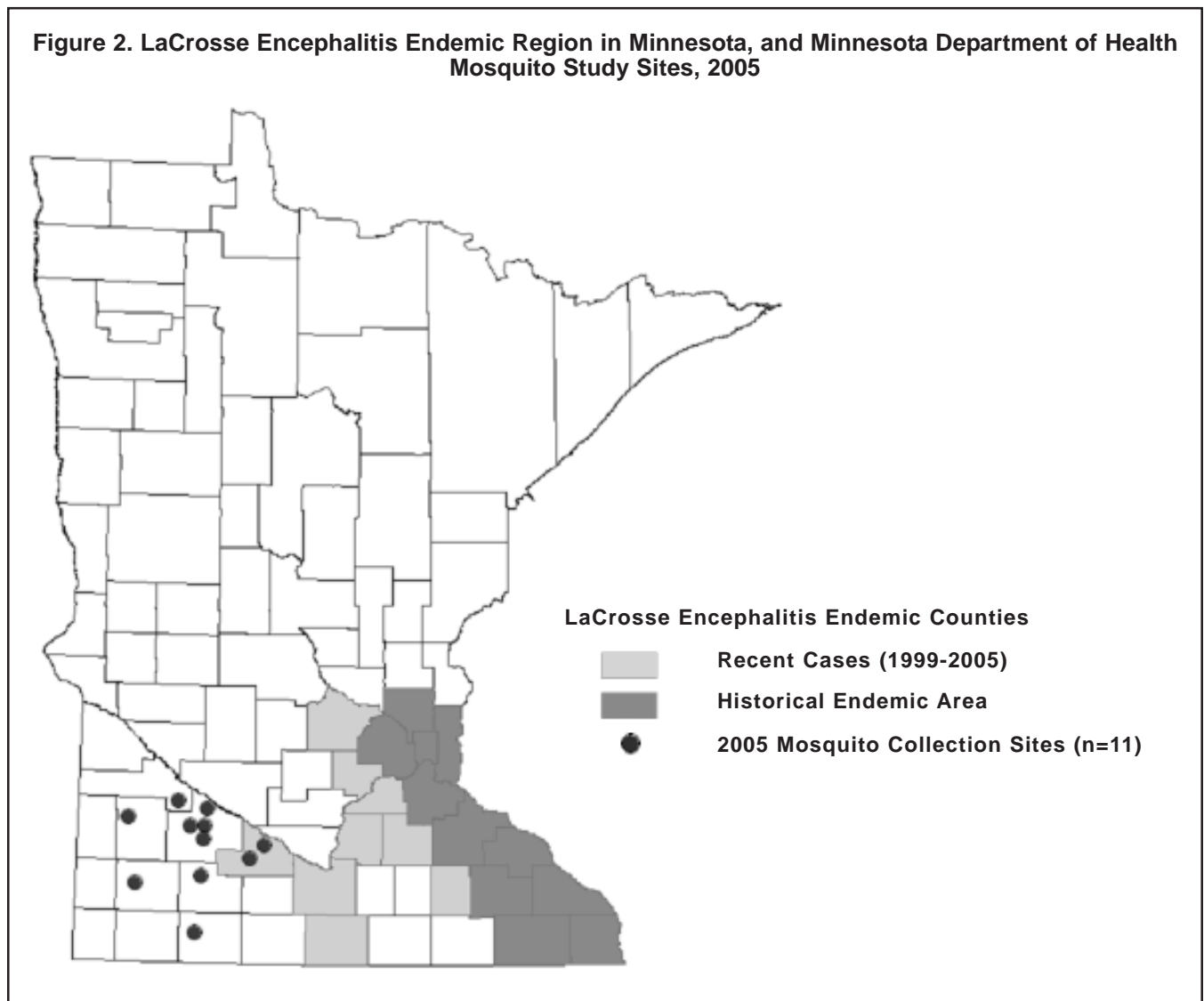
ease risk zone (Figure 1). Field staff collected ticks by dragging a 1 m² white canvas cloth along specific sampling transects and periodically removing any attached ticks.

I. scapularis ticks were identified at 13 of the 16 study sites (Figure 1). Nearly 250 ticks (approximately 160 adults and 90 nymphs) were collected and tested for *B. burgdorferi*, *A. phagocytophilum*, and *B. microti*. Overall, 34% of ticks from nine study sites (range, 20-50) were PCR-positive for at least one disease agent (although tick abundance was too low at some sites to determine infection rates with any degree of precision). A smaller percentage of nymph ticks (16%) than adult ticks (44%) were positive; however, nymphs pose a greater disease risk because they are smaller and more difficult to detect. Evidence of all

three pathogens was detected. At a site in Hubbard County, for example, 21 of 36 (58%) adult ticks were positive for *B. burgdorferi*, 8 (22%) for *A. phagocytophilum*, and 4 (11%) for *B. microti*. Simultaneous transmission of these disease agents by ticks with multiple infections can result in coinfections. Further MDH research goals include greater delineation of *I. scapularis* distribution and determination of infection rates.

Medical providers who see patients who live, work, or recreate in these newly determined endemic areas of the state need to be aware that the areas pose an exposure risk. Human exposure risk is greatest in the late spring, early summer, and autumn, when nymph and adult *I. scapularis* ticks quest for blood meals in the leaf litter or herb/shrub layers of hardwood

Figure 2. LaCrosse Encephalitis Endemic Region in Minnesota, and Minnesota Department of Health Mosquito Study Sites, 2005



forests. People visiting these areas should be advised to use personal protection measures such as tick repellents, protective clothing, and prompt inspection and removal of attached ticks.

La Crosse Encephalitis

La Crosse encephalitis (LAC) is endemic in southeastern Minnesota along the Mississippi River valley, from the Iowa border north through the western Twin Cities metropolitan area. However, in recent years most LAC case-patients likely were exposed just west of the traditional endemic area, including the farming regions of Brown and Faribault counties (Figure 2). The primary LAC vector, *Oc. triseriatus*, is a woodland mosquito species that is found exclusively in shaded areas and rarely travels more than 200 meters from the water-holding containers (e.g., waste tires, buckets) or wet tree holes where it hatched.

The landscape of southwestern Minnesota, formerly dominated by tallgrass prairie, is primarily open agricultural land, but includes many small wooded areas between farm fields and around homes. The only large forested areas in the region are found along its rivers and its few lakes. The apparent westward spread of LAC cases, combined with reported exposures from marginal habitat for *Oc. triseriatus*, raises the

question of whether the virus could continue to move westward and become established in parts of the state where it has never been previously detected.

To evaluate *Oc. triseriatus* distribution in southwestern Minnesota, MDH conducted mosquito sampling in seven counties during July and August of 2005 (Figure 2). The collections took place over 6 weeks on 11 wooded sites (six on farms, three in state parks, and two in municipal parks). Sampling involved weekly mosquito egg collections using ovitraps and adult mosquito collections using a battery-powered aspirator. Adult mosquitoes found at the sites or reared from eggs found at the sites were tested for LAC virus by PCR.

Oc. triseriatus eggs and/or adult mosquitoes were found at all 11 sites. The highest adult mosquito counts were from farms. On three of the farms, high numbers of mosquitoes were collected from numerous man-made containers, especially waste tires. Mosquito numbers at these sites rivaled numbers from high-risk sites in southeastern Minnesota. Egg numbers, however, were low at most of the 11 sites, but were higher at locations that lacked man-made containers. (Containers often compete with

ovitraps as mosquito breeding habitat, thus artificially lowering egg counts in the ovitraps.) The lowest adult *Oc. triseriatus* counts were in the three state parks that were tested; no adult mosquitoes were collected in two of those parks. No mosquitoes at any of the 11 sites were PCR-positive for LAC virus.

These data suggest that low-level *Oc. triseriatus* populations are widespread throughout southwestern Minnesota. On farms, which often lack natural habitat, mosquito populations are greatly aided by the presence of artificial containers that hold water and support *Oc. triseriatus* reproduction. If LAC virus were introduced to southwestern Minnesota through the importation of infected eggs in artificial containers, sufficient breeding habitat could allow the virus to become established in localized areas. The recent LAC case reported in Faribault County was on a farm that had several water-holding buckets and other containers brought there from a wooded location in LAC-endemic Houston County.

Medical providers who have pediatric patients (LAC occurs almost exclusively in people 16 years of age or younger) from southwestern Minnesota presenting with viral encephalitis from July through September should consider testing for LAC during the diagnostic process.

Disease Control Newsletter to Cease Publication

The Minnesota Department of Health (MDH) Commissioner's Executive Office has recently prohibited all printed MDH newsletters. One more issue of this *Disease Control Newsletter (DCN)*, including the annual summary of communicable diseases, will be published and distributed later in 2006. We seriously regret this event.

The first issue of the *Communicable Disease Newsletter* was published in January 1974. Articles included were a notice of an ongoing increase in shigellosis cases, a late start to the influenza season, an increase in immunization rates among those entering school, a review of the use of isoniazid for preventive therapy for tuberculosis, and a high number (>400) of positive rabies tests in

animals. Prior to this newsletter was *Minnesota's Health*, and we suspect that some form of published newsletter has been distributed continuously by the MDH since Commissioner of Health Dr. Charles Hewitt began publishing *Public Health in Minnesota* in 1885. In January 1976, the newsletter was renamed the *DCN*, as it is today. Its contents were broadened to include topics other than communicable diseases. Indeed, in the first issue was a lead article on fatal snowmobile accidents.

The *DCN* has been MDH's primary means of reaching physicians and other healthcare providers in the state to describe disease trends, emerging diseases and issues, immunization and other preventive recommenda-

tions, new therapies, and other public health issues. The newsletter is currently mailed free of charge to over 14,000 licensed physicians in Minnesota as well as another 3,500 healthcare providers.

Many newsletters have gone to an electronic format. However, after thoroughly investigating this possibility, we concluded that we would fail to reach a vast majority of the intended audience of this newsletter by relying on email distribution or email notification and posting on a website. The *DCN* articles have been written and edited for a printed version. We will continue to research other avenues to reach you the readers of the *DCN*. Your support as readers has been appreciated.

New In Vitro Blood Test for Tuberculosis*

If not detected and treated, latent tuberculosis (TB) infection (LTBI) develops into active TB disease in approximately 10% of infected persons with normal immune systems. The risks are higher for young children and persons with recent infection, certain medical conditions, or chest radiograph findings suggestive of previous TB. Because treatment for LTBI can be up to 90% effective in preventing the progression of LTBI to active TB, the detection and treatment of LTBI is an important strategy in efforts to control and prevent TB. In addition, the risk of TB transmission in the community is decreased when persons with active TB disease are identified and treated in a timely manner. Although the tuberculin skin test (TST) is an aid to diagnosing active TB, up to 25% of persons with active TB disease have a negative TST at the time of diagnosis.

New In Vitro Blood Test

Clinicians and public health professionals have long recognized the need for improved methods for identifying persons infected with TB. Since its development in the 1930s, the TST has been the only available method for identifying latent TB infection. The test has significant limitations, including the need for two office visits to administer and read the test; biases and errors in administering, reading and interpreting the test; false positive results due to prior Bacille Calmette-Guerin (BCG) vaccination or infection with nontuberculous mycobacteria; and false negative results due to anergy, immune suppression, or overwhelming TB disease.

In December 2005, the Centers for Disease Control and Prevention (CDC) published interim guidelines for the use of a new in vitro blood test, QuantiFERON-TB Gold (QFT-G), as an aid for diagnosing LTBI and TB disease. QFT-G has significant improvements over the original QuantiFERON (QFT) test approved in 2001, which was not widely used and is no longer commercially available. The new guidelines are intended to help public health officials, clinicians and laboratorians understand how to interpret the QFT-G test and assess its potential for use in TB control efforts.

QFT-G is an enzyme-linked immunosorbent assay (ELISA) test that detects the release of interferon-gamma (IFN-g) in blood from sensitized persons when it is incubated for 16-24 hours with mixtures of synthetic peptides representing two proteins present in *Mycobacterium tuberculosis*. Test results are based on the amount of IFN-g that is released during this process. The new guidelines indicate that QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of healthcare workers and others undergoing serial evaluation for *M. tuberculosis* infection. QFT-G usually can be used in place of (and not in addition to) the TST.

Advantages of the QFT-G Test

The test's advantages include the following.

- It can be used for diagnosing both LTBI and active TB disease, whereas the QFT was approved only for use in diagnosing LTBI.
- Because the antigens used in the QFT-G test are more specific for *M. tuberculosis* than is the tuberculin used in the TST, there is less chance of false-positive results due to previous BCG vaccination or nontuberculous mycobacteria such as *M. avium*. This could be a distinct advantage in Minnesota, where most TB occurs among foreign-born individuals, many of whom have received BCG vaccination overseas.
- Results are available less than 24 hours after testing, eliminating the second office visit.
- It does not cause "boosting" because, unlike the TST, no antigen is injected into the body.
- As a blood test, it is not subject to the biases and errors of TST placement and reading.
- It might be a cost-effective alternative to the TST in testing programs that are part of the infection control program in institutions such as healthcare settings, correctional facilities, or homeless shelters.

Limitations of the QFT-G Test

The test's limitations include the following.

- Blood samples must be processed within 12 hours of collection. A future generation of the test is expected to address this issue.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the test's accuracy.
- As with the TST, it cannot differentiate between TB disease and LTBI.
- Collecting the required 5-ml sample of blood from young children may not be possible or acceptable.
- Similar to any other diagnostic test, the predictive value of QFT-G results depends on the prevalence of *M. tuberculosis* infection in the population being tested.
- The significance of indeterminate QFT-G results has not been determined.

Issues Requiring Further Study

In addition to the above limitations, several issues have not yet been studied extensively, including:

- Its sensitivity for particular groups of TB patients (e.g., young children and immunocompromised patients) has not been determined.
- Its sensitivity for LTBI might be less than that of the TST, although the lack of a confirmatory test makes this difficult to assess.
- The ability of QFT-G to predict risk for LTBI progressing to TB disease has not been determined.
- Published data are relatively limited concerning the use of QFT-G among persons recently exposed to TB (e.g., contacts) and other populations at high risk for LTBI.
- No published data document the performance of QFT-G in children under the age of 17 years.

Post-test Evaluations

The majority of healthy adults who have negative QFT-G results are unlikely to have *M. tuberculosis* infection and do not require further evaluation. A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. Whenever LTBI or TB disease is being diagnosed by any method, clinicians

should coordinate their efforts with state or local public health TB control programs. Persons with positive QFT-G results, regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed and treatment is initiated. As with the TST, persons with signs and symptoms of active TB disease should undergo additional diagnostic evaluation before or at the same time as the QFT-G. These should not be delayed while awaiting QFT-G results. Evaluations should include chest radiography, bacteriologic studies, serology for HIV, and, as indicated by the illness, additional tests and studies.

Confirming or excluding TB disease and assessing the probability of LTBI require a combination of epidemiologic, historic, physical, and diagnostic findings that should be considered when interpreting QFT-G or TST results. With any of the testing methods, persons who have a negative test result can still have LTBI. Those who have a negative result but who are likely to have LTBI and who are at greater risk for severe illness or poor outcomes if TB disease occurs might need treatment or closer monitoring for disease. Potential examples include close contacts who are under the age of 5 years, those who are immunocompromised because of HIV infection, or those who will undergo treatment with TNF- α antagonists

(which increase the risk for progression from LTBI to TB disease).

Investigating Contacts

The guidelines recommend that TB control programs can use QFT-G for investigating contacts of persons with potentially infectious TB disease. Because it does not require a second visit to complete, test results likely will be available from a greater percentage of contacts than would be available using TST. Because QFT-G is more specific than the TST, it is expected to indicate a smaller proportion of contacts as infected than the TST would indicate. Public health resources that previously were devoted to completing skin testing can instead be concentrated on full evaluation and complete treatment of contacts who have positive QFT-G results. In contrast to the TST, initial QFT-G testing of contacts will not boost subsequent test results; thus, uncertainty about interpreting follow-up results is avoided.

Proper Handling of Specimens

TB control programs or institutions that elect to use QFT-G should consult and collaborate with laboratories in their system to ensure that specimens are properly obtained, handled, and processed prior to and after arrival in the laboratory. Training of laboratory staff will be necessary. Certain facilities might elect to refer specimens for test-

ing. The Clinical Laboratory Improvement Amendments (CLIA) regulations for quality systems of all phases of the total testing process (pre-analytic, analytic, and post-analytic) and for general laboratory systems must be followed.

Availability in Minnesota

QFT-G is not widely available in Minnesota at this time. MDH is attempting to gather information regarding facilities that offer the test currently or that plan to do so. At the time of publication of this newsletter, MDH is aware of only one facility in Minnesota that currently offers the QFT-G test. Two facilities have indicated that they plan to implement QFT-G testing later in 2006.

CDC is working with partners and the manufacturer to develop educational materials for physicians regarding the use of the QFT-G assay. For additional information about QFT-G, the complete report can be obtained at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

*Adapted from: Mazurek GH, Jereb J, LoBue P, Iademarco MF, Metchock B, Vernon A. Guidelines for using the QuantiFERON[®]-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR Morb Mortal Wkly Rep.* 2005;54(No. RR-15);49-55. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm.

Revised National Tuberculosis Infection Control Guidelines*

In 1994, the Centers for Disease Control and Prevention (CDC) published the "Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in HealthCare Facilities, 1994." The guidelines were issued in response to 1) a resurgence of tuberculosis (TB) disease that occurred in the United States in the mid-1980s and early 1990s, 2) the documentation of several high-profile healthcare-associated (previously termed "nosocomial") outbreaks related to an increase in the prevalence of TB disease and human immunodeficiency virus (HIV) coinfection, 3) lapses in infection control practices, 4) delays in the diagnosis and treatment of persons with infectious TB disease, and 5) the ap-

pearance and transmission of multidrug-resistant (MDR) TB strains. The 1994 guidelines, which followed statements issued in 1982 and 1990, presented recommendations for TB infection control based on a risk assessment process that classified healthcare facilities according to categories of TB risk, with a corresponding series of administrative, environmental, and respiratory protection control measures.

The TB infection control measures recommended by CDC in 1994 were implemented widely in healthcare facilities in the United States. The result has been a decrease in the number of TB outbreaks in healthcare settings

reported to CDC and a reduction in healthcare-associated transmission of *M. tuberculosis* to patients and healthcare workers. Concurrent with this success, mobilization of the nation's TB control programs succeeded in reversing the upsurge in reported cases of TB disease, and case rates have declined in the subsequent 10 years. Findings indicate that although the 2004 TB rate was the lowest recorded in the United States since national reporting began in 1953, the declines in rates for 2003 (2.3%) and 2004 (3.2%) were the smallest since 1993.

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Despite the general decline in TB rates in recent years, a marked geographic variation in TB case rates persists, which means that healthcare workers in different areas face different risks. In 2004, case rates varied per 100,000 population: 1.0 in Wyoming, 7.1 in New York, 8.3 in California, and 14.6 in the District of Columbia. There were 3.9 cases of TB per 100,000 in Minnesota in 2004. In addition, despite the progress in the United States, the 2004 rate of 4.9 per 100,000 population remained higher than the 2000 goal of 3.5. This goal was established as part of the national strategic plan for TB elimination; the final goal is <1 case per 1,000,000 population by 2010. In addition, TB infection rates greater than the U.S. average continue to be reported in certain racial/ethnic populations. The threat of MDR TB is decreasing, and the transmission of *M. tuberculosis* in healthcare settings continues to decrease because of implementation of infection control measures and reductions in community rates of TB.

Given the changes in epidemiology and a request by the Advisory Council for the Elimination of Tuberculosis (ACET) for review and update of the 1994 TB infection control document, CDC has reassessed the TB infection control guidelines for healthcare settings. This report updates TB control recommendations reflecting shifts in the epidemiology of TB, advances in scientific understanding, and changes in healthcare practice that have occurred in the United States during the preceding decade. In the context of diminished risk for healthcare-associated transmission of *M. tuberculosis*, this document places emphasis on actions to maintain momentum and expertise needed to avert another TB resurgence and to eliminate the lingering threat to healthcare workers, which is mainly from patients or others with unsuspected and undiagnosed infectious TB disease.

Broader Definition of Healthcare Setting

The new guidelines have been expanded to address a broader concept; healthcare-associated settings go beyond the previously defined facilities. The term “setting” has been chosen over the term “facility,” used in the previous guidelines, to broaden the potential places for which these guidelines apply.

“Setting” is used to describe any relationship (physical or organization) in which healthcare workers might share air space with persons with TB disease or in which healthcare workers might be in contact with clinical specimens. Various setting types might be present in a single facility. Healthcare settings include inpatient settings, outpatient settings, and nontraditional facility-based settings.

- Inpatient settings include patient rooms, emergency departments, intensive care units, surgical suites, laboratories, laboratory procedure areas, bronchoscopy suites, sputum induction or inhalation therapy rooms, autopsy suites, and embalming rooms.
- Outpatient settings include TB treatment facilities, medical offices, ambulatory-care settings, dialysis units, and dental-care settings.
- Nontraditional settings include emergency medical service, medical settings in correctional facilities, home-based healthcare and outreach settings, long-term-care settings, hospice settings, and homeless shelters. Other settings in which suspected and confirmed TB patients might be encountered might include cafeterias, general stores, kitchens, laundry areas, maintenance shops, pharmacies, and law enforcement settings.

Changes from Previous Guidelines

CDC prepared the guidelines in this report in consultation with experts in TB, infection control, environmental control, respiratory protection, and occupational health. This report replaces all previous CDC guidelines for TB infection control in healthcare settings. The following changes differentiate this report from previous guidelines:

- The risk assessment process includes the assessment of additional aspects of infection control.
- The term “tuberculin skin tests” (TSTs) is used instead of purified protein derivative (PPD).
- The whole-blood interferon gamma release assay (IGRA), QuantiFERON®TB Gold test (QFTG) (Cellestis Limited, Carnegie, Victoria, Australia), is a Food and Drug Administration (FDA)-approved in vitro cytokine-based assay for cell-mediated immune reactivity to *M. tuberculosis* and might be used instead of TST in TB screening programs for healthcare workers. This IGRA is

an example of a blood assay for *M. tuberculosis* (BAMT).

- The frequency of TB screening for healthcare workers has been decreased in various settings, and the criteria for determination of screening frequency have been changed.
- The scope of settings in which the guidelines apply has been broadened to include laboratories and additional outpatient and nontraditional facility-based settings.
- Criteria for serial testing for *M. tuberculosis* infection of healthcare workers are more clearly defined. In certain settings, this change will decrease the number of healthcare workers who need serial TB screening.
- These recommendations usually apply to an entire healthcare setting rather than to areas within a setting.
- New terms, airborne infection precautions (airborne precautions) and airborne infection isolation room (All room), are introduced.
- Recommendations for annual respirator training, initial respirator fit testing, and periodic respirator fit testing have been added.
- The evidence of the need for respirator fit testing is summarized.
- Information on ultraviolet germicidal irradiation (UVGI) and room-air recirculation units has been expanded.
- Additional information regarding MDR TB and HIV infection has been included.

Incorporating the Recommendations in Minnesota

The Minnesota Department of Health TB Prevention and Control Program will work with other state agencies and programs to review and revise, as needed, current TB-related rules and statutes governing facilities for which there are facility-specific regulations, including long-term care facilities, correctional facilities, hospice, and home care agencies. Minnesota OSHA also is revising its TB directive to incorporate the 2005 recommendations.

* Adapted from: Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare settings, 2005. *MMWR Recomm Rep.* 2005;54(RR-17):1-141. Available online at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm.

Revised Recommendations for the Treatment of Infants Born to Hepatitis B-Infected Women

Revised national recommendations for the treatment of perinatal hepatitis B disease were recently issued by the Advisory Committee on Immunization Practices (ACIP) as part of a broader set of recommendations covering hepatitis B prevention among infants, children, and adolescents.* These guidelines, "A Comprehensive Immunization Strategy to Eliminate Hepatitis B Virus Infection in the United States," update previous recommendations published in November 1991. The new recommendations, which were developed to improve prevention of perinatal and early childhood hepatitis B virus (HBV) transmission, include implementation of universal infant vaccination beginning at birth and activities to increase vaccine coverage among previously unvaccinated children and adolescents.

Despite the decline in hepatitis B incidence in the United States, challenges remain to eliminate perinatal and childhood HBV transmission. The Centers for Disease Control and Prevention estimates that only about half of expected births to hepatitis B surface antigen (HBsAg)-positive women are identified for case management; such identification is needed to maximize on-time delivery of postexposure immunoprophylaxis. In addition, errors in management of infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status have kept many of these infants from receiving appropriate immunoprophylaxis to prevent HBV infections. The Minnesota Department of Health (MDH) perinatal hepatitis B prevention program identified seven infants born to hepatitis B-infected women during 2004 and three infants born to hepatitis B-infected women during 2005 who were not identified by birthing hospital staff and did not receive appropriate immunoprophylaxis before hospital discharge. The reasons these infants were not identified include transcription errors, misreading of laboratory results, and lack of knowledge of appropriate treatment for infants born to mothers of unknown HBsAg status.

Following are some highlights from the new ACIP statement pertaining to prevention of perinatal HBV infection and the management of pregnant women.

Prenatal HBsAg Testing

- All pregnant women should be tested routinely for HBsAg during an early prenatal visit (e.g., first trimester) during each pregnancy, even if they have been previously vaccinated or tested.
- Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., injection-drug use, having had more than one sex partner in the previous 6 months or an HBsAg-positive sex partner, or evaluation or treatment for a sexually transmitted disease [STD] or for recent or current injection-drug use) and those with clinical hepatitis should be tested at the time of admission to the hospital for delivery.
- All laboratories that provide HBsAg testing of pregnant women should use an HBsAg test licensed and approved by the Food and Drug Administration and should perform testing according to the manufacturer's labeling, including testing of initially reactive specimens with a licensed neutralizing confirmatory test. When pregnant women are tested for HBsAg at the time of admission for delivery, shortened testing protocols may be used and initially reactive results reported to expedite administration of immunoprophylaxis to infants.
- Women who are HBsAg positive should be referred to an appropriate case management program to ensure that their infants receive timely postexposure prophylaxis and follow-up. In addition, a copy of the original laboratory report indicating the pregnant woman's HBsAg status should be provided to the hospital where delivery is planned and to the healthcare provider who will care for the newborn.
- Women who are HBsAg positive should be provided with or referred for appropriate counseling

and medical management.

HBsAg-positive pregnant women should receive information concerning hepatitis B that discusses

- modes of transmission;
- perinatal concerns (e.g., infants born to HBsAg-positive mothers may be breastfed);
- prevention of HBV transmission to contacts, including the importance of postexposure prophylaxis for the newborn infant and hepatitis B vaccination for household, sexual, and needle-sharing contacts;
- substance abuse treatment, if appropriate; and
- medical evaluation and possible treatment of chronic hepatitis B.

• When HBsAg testing of pregnant women is not feasible (i.e., in remote areas without access to a laboratory), all infants should receive hepatitis B vaccine ≤ 12 hours after birth and should complete the hepatitis B vaccine series according to a recommended schedule for infants born to HBsAg-positive women (Table 1).

Management of Infants Born to Women Who Are HBsAg Positive

- All infants born to HBsAg-positive women should receive single-antigen hepatitis B vaccine and hepatitis B immune globulin (HBIG) (0.5 mL) ≤ 12 hours after birth, administered at different injection sites. The vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (Table 1). The final dose in the vaccine series should not be administered before age 24 weeks (164 days).
- For preterm infants weighing less than 2,000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches age 1 month.

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- Postvaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 9-18 months (generally at the next well-child visit). Testing should not be performed before age 9 months to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti-HBc testing of infants is not recommended because passively acquired maternal anti-HBc might be detected in infants born to HBV-infected mothers to age 24 months.
 - HBsAg-negative infants with anti-HBs levels ≥ 10 mIU/mL are protected and need no further medical management.
 - HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1-2 months after the final dose of vaccine.
 - Infants who are HBsAg positive should receive appropriate follow-up.
- Infants of HBsAg-positive mothers may be breast fed beginning immediately after birth.
- Although not indicated in the manufacturer's package labeling, HBsAg-containing combination vaccines may be used for infants aged ≥ 6 weeks old and born to HBsAg-positive mothers to complete the vaccine series after receipt of a birth dose of single-antigen hepatitis B vaccine and HBIG.

Management of Infants Born to Women with Unknown HBsAg Status

- Women admitted for delivery without documentation of HBsAg test results should have blood drawn and tested as soon as possible after admission.
- While test results are pending, all infants born to women without documentation of HBsAg test results should receive the first dose of single-antigen hepatitis B vaccine (without HBIG) ≤ 12 hours of birth.
 - If the mother is determined to be HBsAg positive, her infant should receive HBIG as soon as possible but no later than age 7 days, and the vaccine series should be completed according to a recommended

schedule for infants born to HBsAg-positive mothers (Table 1).

- If the mother is determined to be HBsAg negative, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-negative mothers (Table 1).
- If the mother has never been tested to determine her HBsAg status, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (Table 1).
- Administration of HBIG is not necessary for these infants.

Vaccination of Pregnant Women

- Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., having more than one sex partner during the previous 6 months, been evaluated or treated for an STD, recent or current injection-drug use, or having had an HBsAg-positive sex partner) should be vaccinated.
- Pregnant women at risk for HBV infection during pregnancy should be counseled concerning other methods to prevent HBV infection.

Delivery Hospital Policies and Procedures

- All delivery hospitals should implement policies and procedures to ensure 1) identification of infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status (see Prenatal HBsAg Testing), and 2) initiation of immunization for these infants. Such policies and procedures should include the following standing orders:
 - for all pregnant women, a review of HBsAg test results at the time of admission for delivery;
 - for women who do not have a documented HBsAg test result, HBsAg testing as soon as possible after admission for delivery;
 - identification and management of all infants born to HBsAg-positive mothers;
 - identification and management of all infants born to mothers with unknown HBsAg

status; and

- for all infants, documentation on the infant's medical record of maternal HBsAg test results, infant hepatitis B vaccine administration, and administration of HBIG (if appropriate).
- Delivery hospitals should enroll in the federally funded Vaccines for Children (VFC) program to obtain free hepatitis B vaccine for administration of the birth dose to newborns who are eligible (i.e., Medicaid eligible, American Indian or Alaska Native, underinsured, or uninsured). (For information about Minnesota's VFC program, call the MDH Immunization Hotline at 1-800-657-3970 or 651-201-5503.)

Universal Vaccination of Infants

- All infants should receive the hepatitis B vaccine series as part of the recommended childhood immunization schedule.
- For all medically stable infants weighing $\geq 2,000$ g at birth and born to HBsAg-negative mothers, the first dose of vaccine should be administered before hospital discharge. Only single-antigen hepatitis B vaccine should be used for the birth dose.
- On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs $\geq 2,000$ g and whose mother is HBsAg negative.
 - When such a decision is made, a physician's order to withhold the birth dose and a copy of the original laboratory report indicating that the mother was HBsAg negative during this pregnancy should be placed in the infant's medical record.
 - For infants who do not receive a first dose before hospital discharge, the first dose should be administered no later than age 2 months.
 - Situations in which the birth dose should not be delayed include any high-risk sexual or drug-using practices of the infant's mother during pregnancy (e.g., having had more than one sex partner during the previous 6 months or an HBsAg-positive sex partner, evaluation or treatment for an

STD, or recent or current injection-drug use) and expected poor compliance with follow up to initiate the vaccine series.

- Preterm infants weighing less than 2,000 g and born to HBsAg-negative mothers should have their first vaccine dose delayed until 1 month after birth or hospital discharge. For these infants, a copy of the original laboratory report indicating that the mother was HBsAg negative during this pregnancy should be placed in the infant's medical record.
- The vaccine series should be completed according to a recommended schedule with either single-antigen vaccine or a combination vaccine that contains the hepatitis B vaccine antigen (e.g., Hib-hepatitis B or DTaP-IPV-hepatitis B). The final dose in the vaccine series should not be administered before age 24 weeks (164

days).

- Administration of 4 doses of hepatitis B vaccine to infants is permissible in certain situations (e.g., when combination vaccines are administered after the birth dose).
- In populations with currently or previously high rates of childhood HBV infection (i.e., Alaska Natives; Pacific Islanders; and immigrant families from Asia, Africa, and other regions with intermediate or high endemic rates of infection), the first dose of hepatitis B vaccine should be administered at birth and the final dose at age 6-12 months.

The Minnesota Perinatal HBV Prevention Program

MDH has a close partnership with local health departments statewide to provide comprehensive case management for infants born to HBsAg-positive mothers, ensuring that they receive

timely postexposure prophylaxis and follow up. For more information on the Minnesota Perinatal HBV Prevention Program, contact the MDH immunization hotline at 800-657-3970 or visit the MDH Web site at: www.health.state.mn.us/hepatitis. (Click on the link entitled "Perinatal Hepatitis B" listed in the right-hand navigation bar.) The link to the updated ACIP recommendations can be found there.

* Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep*. 2005;54(RR16):1-31. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm.

Table 1. Hepatitis B Vaccine and Hepatitis B Immune Globulin (HBIG) Schedules for Newborn Infants, by Maternal Hepatitis B Surface Antigen (HBsAg) Status

Maternal HBsAg Status	Single-antigen vaccine		Single antigen + combination vaccine	
	Dose	Age	Dose	Age
Positive	1*	Birth (≤12 hours)	1*	Birth (≤12 hours)
	HBIG†	Birth (≤ 12 hours)	HBIG	Birth (≤12 hours)
	2	1-2 mos	2	2 mos
	3‡	6 mos	3	4 mos
Unknown§	1*	Birth (≤12 hours)	1*	Birth (≤12 hours)
	2	1-2 mos	2	2 mos
	3‡	6 mos	3	4 mos
			4‡	6 mos (Pediarix) or 12-15 mos (Comvax)
Negative	1*, ¶	Birth (≤12 hours)	1*, ¶	Birth (≤12 hours)
	2	1-2 mos	2	2 mos
	3‡	6-18 mos	3	4 mos
			4‡	6 mos (Pediarix) or 12-15 mos (Comvax)

* Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediarix cannot be administered at birth or before age 6 weeks.

† Hepatitis B immune globulin (0.5 mL) administered intramuscularly in a separate site from vaccine.

‡ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

§ Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.

¶ On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 g and whose mother is HBsAg negative, but only if a physician's order to withhold the birth doses and a copy of the mother's original HBsAg-negative laboratory report are documented in the infant's medical record.

Save the Dates: November 2 and 3 (half-day), 2006 12th Annual Emerging Infections in Clinical Practice and Public Health Conference, Minneapolis

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