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Outbreaks: West Nile Virus, Rift Valley Fever, and Ebola Virus Infection—What and Where Next?

ABSTRACTS & COMMENTARY

Synopsis: *These three viral infections keep expanding their areas of activity.*

Sources: CDC. Outbreak of Rift Valley fever—Saudi Arabia, August-October, 2000. *MMWR Morb Mortal Wkly Rep* 2000;49:905-908; Ebola hemorrhagic fever in Uganda—Update. http://www.who.int/disease-outbreak-news/; West Nile Virus, http://www.promedmail.org.

An outbreak of haemorrhagic fever in saudi arabia, which had affected more than 450 individuals by October 26th, has been demonstrated to be due to Rift Valley Fever (RVF) virus. The diagnosis was confirmed by the Centers for Disease Control (CDC) using multiple methodologies, including ELISA antigen detection and IgM antibody tests, PCR, and immunohistocytochemistry. Eighty-eight (20%) of those affected have died. Affected individuals had resided in or visited the floodplains of the wadis, or seasonal riverbeds, in the southwestern area of Saudi Arabia. The adjacent area of Yemen was also affected with a total of 706 cases and 97 deaths.

Outbreaks of RVF in ruminants and humans are associated with periodic heavy rainfalls in otherwise arid areas. Its transmission to humans is predominantly by the bite of infected *Aedes* and *Culex* mosquitoes, as well as by contact with infected animal body fluids.

This is the first report of acquisition of RVF outside of Africa, but its location is not surprising. The Rift Valley, from which the virus takes its name, is a geological feature that extends 6500 kilometers from the coast of Mozambique all the way to the Dead Sea. The most recent outbreak of this infection occurred in Kenya in 1997-1998 and was associated with more than 300 human fatalities.[1]

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Symptomatic infection with this phlebovirus is associated, after an incubation period of 3-7 days, with fever, headache, arthralgias, myalgias, and photophobia. The vast majority of cases are uncomplicated and self-limited. Several percent of those affected develop macular and perimacular retinitis with vasculitis, a complication that may cause permanent blindness. Encephalitis may also occur. Approximately 1% develop fulminant hemorrhagic fever. Ribavirin therapy has been reported to be effective in animal models of infection, but its efficacy in human infection is unknown. An inactivated RVF vaccine has been reported to be safe and immunogenic in humans.[2]

Ebola Virus

As of October 29th, the Ministry of Health of Uganda had reported 211 cases of haemorrhagic fever, including 72 deaths from Gulu province. Laboratory testing carried out at the National Institute of Virology in South Africa indicates that the cause of the outbreak is the Ebola virus. These are the first cases of Ebola ever reported in Uganda.

The Associated Press reported that one of the first recognized victims of this outbreak was Esther Awate, who died on September 7. In keeping with custom, her body was kept in her hut for two days and ritually bathed by family and close friends before burial. Ms. Awate's mother, 9-month-old child, and six other relatives have since also died. An 8-year-old son who did not take part in the funeral ritual has survived.

Laurie Garrett reported that another early victim was an infant in Kabede Opon whose family had fled the Lord's Resistance Army, a terrorist group based in Sudan. Kabede Opon is just a few miles from Gulu (225 miles north of Kampala) and is only 200 kilometers from Maridi, Sudan, where Ebola outbreaks had occurred in 1976 and 1979.

Ebola is a filovirus that causes sporadic infections and periodic outbreaks of infection in Africa, as in the large 1998 outbreak in Kikwit, Zaire.[3] The illness usually begins abruptly, after a usual incubation period of 4-10 days, with fever, headache, arthralgia, and myalgia. Bradycardia, pharyngitis, and conjunctivitis may also occur, as well as a measle-like skin eruption. With progression, hematemesis and other hemorrhagic manifestations occur. The reported usual fatality rate is as high as 90% although it appears to be only 34% in the current outbreak.

The endemic reservoir of Ebola virus appears to be small rodents, but during outbreaks it is also transmitted between humans by direct contact with body fluids. The burial practices of affected populations, especially the ritual bathing, are believed to play an important role in many cases.

Recent experimental studies have improved our understanding of this infection. Interferon production is inhibited by Ebola infection by a mechanism involving viral VP35 protein.[4] The Ebola secretory glycoprotein alters the physical linkage between neutrophil FcγRIIIB (CD16b) and CR3, inhibiting L-selectin shedding.[5] Ebola glycoprotein is also associated with endothelial damage and, presumably, is critical to the pathogenicity of the virus, contributing to the haemorrhagic manifestations of infection.[6] Thus, secreted glycoprotein inhibits early neutrophil activation, which likely affects the host response to infection, as does the effect of VP135 on interferon production. In addition, binding of the transmembrane glycoprotein to endothelial cells may contribute to the haemorrhagic symptoms of this disease.[7]

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Studies in primates suggest that the lymphocytopenia seen in Ebola infection is associated with lymphocyte apoptosis.[8] Fatal Ebola infection is associated with impaired antibody response and, in the last five days of life, with massive intravascular apoptosis with disappearance of T-cell mediated mRNA.[9]

Protective monoclonal antibodies against epitopes of the Ebola glycoprotein, including one epitope that is conserved among all known Ebola strains pathogenic for humans, have been generated.[10] The detection of potentially protective epitopes raises hope for effective vaccine development.

Passive immunoprophylaxis and therapy is also under investigation, as are potential antivirals. A caprine hyperimmune globulin preparation was effective when given 48 hours after infection of guinea pigs.[11] Carbocyclic 3-deazaadenosine, an inhibitor of S-adenosylhomocysteine hydrolase, is effective in a murine model of Ebola infection.[12]

West Nile Virus

West Nile virus (WNV), after making its first U.S. appearance last year, reared its ugly head once again this summer. As of October 28, 18 human cases with one death had been detected, all having occurred within six different counties of New York, New Jersey, and Connecticut.

This flavivirus also affects other mammals and the extent of this involvement has become apparent through active surveillance programs. Almost 3000 birds have been documented as infected with WNV in 2000. The total number of WNV-positive specimens from New York state alone for this year as of October 13th was 1080 birds, 317 mosquito pools, two sentinel chickens, seven live wild birds, 14 bats, eight horses, two cats, two raccoons, three domestic rabbits, three squirrels, one chipmunk, and 13 human cases.

Infected birds were recently detected for the first time in Vermont, Virginia, and North Carolina, having previously been found in Pennsylvania, New York, Rhode Island, District of Columbia, Maryland, Massachusetts, Connecticut, and New Jersey. Infected horses have been detected in New York, Rhode Island, Massachusetts, New Jersey, Connecticut, and Pennsylvania. (Equine infection with WNV has recently occurred for the first time in 40 years in the Camargue region of southern France). Infected mosquitoes have been detected in New York, Pennsylvania, New Jersey, and Massachusetts.

Active surveillance and mosquito abatement measures have kept the number of human cases low. It is anticipated, however, that the virus will be spread to other areas of North America, as well as to areas of South America that are visited by infected birds during their annual migrations.

Treatment of WNV infection is supportive, but recent evidence indicates that ribavirin has inhibitory activity against this virus in human neural cells in vitro.[14] ❖

References

1. Deresinski SC. Outbreak: Rift valley fever in Kenya. *Infectious Disease Alert* 1998;17:68-70.
2. Pittman PR, et al. Immunogenicity of an inactivated Rift Valley fever vaccine in humans: a 12-year experience. *Vaccine* 1999;18:181-189.
3. Deresinski SC. Ebola fever: Where next? *Infectious Disease Alert* 1995;14:134-136.
4. Basler CF, et al. The Ebola virus VP35 protein functions as a type I IFN antagonist. *Proc Natl Acad Sci U S A* 2000;97(22):12289-12294.
5. Kindzelskii AL, et al. Ebola virus secretory glycoprotein (sGP) diminishes Fc gamma RIIIB-to-CR3 proximity on neutrophils. *J Immunol* 2000;164:953-958.
6. Yang ZY, et al. Identification of the Ebola virus glycoprotein as the main viral determinant of vascular cell cytotoxicity and injury. *Nat Med* 2000;6:886-889.
7. Yang Z, et al. Distinct interactions of secreted and transmembrane Ebola virus glycoproteins. *Science* 1998;286:1034-1037.
8. Geisbert TW, et al. Apoptosis induced in vitro and in vivo during infection by Ebola and Marburg viruses. *Lab Invest* 2000;80:171-186.
9. Baize S, et al. Defective humoral responses and extensive intravascular apoptosis are associated with fatal outcome in Ebola virus-infected patients. *Nat Med* 1999;5:423-426.
10. Wilson JA, et al. Epitopes involved in antibody-mediated protection from Ebola virus. *Science* 2000;287: 1664-1666.
11. Kudoyarova-Zubavichene NM, et al. Preparation and use of hyperimmune serum for prophylaxis and therapy of Ebola virus infections. *J Infect Dis* 1999; 179(Suppl 1):S218-S223.
12. Huggins J, Zhang ZX, Bray M. Antiviral drug therapy of filovirus infections: S-adenosylhomocysteine hydrolase inhibitors inhibit Ebola virus in vitro and in a lethal mouse model. *J Infect Dis* 1999;179(Suppl 1): S240-S247.
13. Rappole JH, Derrickson SR, Hubalek Z. Migratory birds and spread of West Nile virus in the Western Hemisphere. *Emerg Infect Dis* 2000;6:19-28.
14. Jordan I, et al. Ribavirin inhibits West Nile virus replication and cytopathic effect in neural cells. *J Infect Dis* 2000;182:1214-1217.

A Protocol for Empiric Treatment of ICU Patients with Pulmonary Infiltrates Reduces Antibiotic Use

ABSTRACT & COMMENTARY

Synopsis: *This randomized trial provides strong evidence for a rational approach to the use of antibiotics in critical care patients with pulmonary infiltrates that is associated with improved outcomes while reducing antimicrobial use.*

Source: Singh N, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162:505-511.

An accurate diagnosis of the cause of pulmonary infiltrates is often difficult in the intensive care unit (ICU) patient. Many patients who do not have pneumonia are treated with antibiotics because of diagnostic uncertainty and clinician anxiety. Singh and colleagues performed a randomized trial comparing a protocol for empiric antibiotic use with usual care in ICU patients with new pulmonary infiltrates. They sought to determine if a brief (3 day) period of administration of a defined empiric protocol would lead to a decrease in antibiotic use without compromising outcome.

Patients with new onset pulmonary infiltrates were evaluated using the clinical pulmonary infection score (CPIS). The CPIS uses six readily accessible clinical variables to determine the likelihood that a patient has pneumonia;[1] these include temperature, leukocyte count, sputum purulence, oxygenation, radiographic findings, and culture. Patients with a CPIS more than 6 were considered likely to have pneumonia, and were excluded from the study. Patients with a CPIS less than 6 were considered less likely to have pneumonia, and randomized. Those in the experimental group received ciprofloxacin 400 mg IV every 8 hours; control patients received usual care from the ICU staff. Patients were re-evaluated in three days. For patients in the protocol group, if the CPIS remained less than 6 and no additional foci of infection were apparent, antibiotics were stopped. If the CPIS was more than 6, antibiotic therapy was continued, subject to modification based on culture results. In both groups, sputum cultures were obtained after therapy. Primary end points were mortality, length of ICU stay, acquisition of resistant organisms, and cost of antimicrobial therapy.

Thirty-nine patients were randomized to the ciprofloxacin group, and 42 to the control group. Mortality, extrapulmonary infections, and the proportion of patients developing a CPIS more than 6 (implying pneumonia) at three days were not significantly different between the groups. Twenty-one percent of the ciprofloxacin group had a CPIS more than 6 at three days, compared with 23% of controls. Antibiotics were continued for more than three days in 28% of the protocol patients compared with 97% of controls (P = 0.0001). Antibiotic therapy was discontinued at three days in all 25 protocol patients with CPIS less than 6 and no evidence of extrapulmonary infection. In contrast, 24 of 25 such patients in the control group continued to receive antibiotics. Antibiotic costs, duration of ICU stay, and recovery of antibiotic resistant organisms from sputum were all significantly lower in protocol patients than in controls.

COMMENT BY ROBERT MUDER, MD

All infectious disease consultants have been in the frustrating position of trying to convince attending physicians that an ICU patient has a low likelihood of pneumonia, and that antimicrobial therapy should be withheld or discontinued. The response is, all too often, completely disregarded or the argument is made that one can't be absolutely sure infection is not present, and, thus, treatment should continue. The result is overuse of antibiotics on a major scale with its attendant costs, adverse effects, and contribution to the selection of resistant organisms.

The study by Singh et al attempts to inject some rationality into clinical practice by dividing patients into low and high probability of pneumonia based on a straightforward clinical grading system. Those patients with a lower likelihood of infection are given a defined course of empiric ciprofloxacin and re-evaluated at three days. If the evidence in favor of pneumonia is not there, or it is argued that since one cannot be 100% certain of the absence of infection, then empiric therapy is stopped. It is notable that this had no adverse effect on outcome. In fact, some important measures of outcome such as length of ICU stay, cost, and acquisition of resistant bacteria were significantly better in the protocol group than in the control group.

A key factor in the success of the protocol was that it allowed use of empiric antibiotics after identification of the infiltrate. This may have had some therapeutic benefit in treating a pneumonia early in its evolution. However, it is quite likely that many of these patients did not have pneumonia in the first place. The major benefit of the brief course of ciprofloxacin might well have been to provide

enough reassurance to clinicians to prevent the unnecessary administration of additional agents. Thus, the study does not, and was not designed to, answer the question of which ICU patient does or does not have pneumonia. Instead, it successfully identifies patients at low risk in whom antibiotics can safely be discontinued after three days, with substantial clinical and economic benefit. ❖

Reference

1. Pugin JR, et al. Diagnosis of ventilator-associated pneumonia by bacterologic analysis of bronchoscopic and non-bronchoscopic "blind" brocheoalvelar lavage fluid. *Am Rev Respir Dis* 1991;143:1121-1129.

Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response

ABSTRACT & COMMENTARY

Synopsis: *The CDC has published a detailed plan for dealing with potential biological and chemical terrorism.*

Source: Khan AS, et al. Biological and chemical terrorism: Strategic plan for preparedness and response. Recommendations of the CDC strategic planning workgroup. *MMWR Morb Mortal Wkly Rep* 2000;49(No. RR04):1-14.

By now many infectious disease and emergency physicians are sick and tired of hearing about the impending wave of bioterrorism. The CDC must be aware of some ennui on our parts as it starts its guidelines for strategic planning with the following quote from Sir Francis Bacon: ". . . and he that will not apply new remedies must expect new evils; for time is the greatest innovator. . ." Indeed, it seems that innovation derives from rage and craziness in our fellow humans who cohabit this planet with us and think bioterrorism represents the lowest expression of humanity.

Go on we must, it seems, to get ready for the inevitable. Thus, the publication of this 14 page set of rationales and recommendations should have an immediate effect on how public health facilities and institutions prepare for biological and chemical terrorism.

The guidelines begin with an Introduction giving a rationale that the public health infrastructure must be prepared for bioterrorism. This section hints at the advantages of "capitalizing on the advances in technology, information systems, and medical sciences."

The section on Vulnerability is straightforward, stating that incidents have already occurred and that the United States is poorly prepared to cope with the rapid responses that will be necessary to minimize injury to our citizens.

The next section emphasizes that covert attacks are more likely than overt terrorists attacks. The delay that would occur with covert attacks probably effects infectious disease physicians more than other aspects of bioterrorism. Consider the example of contagious variola that would not kill people until weeks after the first manifestation of disease. The monograph goes on to implore that public health officials would be the ones to uncover the attack, identify the microorganisms responsible, and prevent further disease.

The next is the most important section for Infectious Disease physicians, entitled Focusing Preparedness Activities. Box 2 (*see Table*) outlines the steps in preparing for biological attacks and box 3 lists the critical biological agents. Of particular interest is Category C under critical agents since it includes agents like Nipah virus, yellow fever, and multidrug-resistant tuberculosis. Of course, terrorism is not necessarily needed to spread multidrug-resistant tuberculosis.

Table

Preparing Public Health Agencies for Biological Attacks

Steps in Preparing for Biological Attacks

- Enhance epidemiologic capacity to detect and respond to biological attacks.
- Supply diagnostic reagents to state and local public health agencies.
- Establish communication programs to ensure delivery of accurate information.
- Enhance bioterrorism-related education and training for health care professionals.
- Prepare educational materials that will inform and reassure the public during and after a biological attack.
- Stockpile appropriate vaccines and drugs.
- Establish molecular surveillance for microbial strains, including unusual or drug-resistant strains.
- Support the development of diagnostic tests.
- Encourage research on antiviral drugs and vaccines.

Source: Khan AS, et al. *MMWR Morb Mortal Wkly Rep* 2000;49:1-14.

In the section Key Focus Areas, the CDC lists their five areas of focus: 1) Preparedness and prevention; 2) detection and surveillance; 3) diagnosis and characterization of biological and chemical agents; 4) response; and 5) communication. There are multiple important developments necessary to achieve the goals of these focus areas. The CDC will help state labs develop a coordinated preparedness plan and response protocols. Diagnostic preparedness will include a multilevel labo-

ratory response network. It will be necessary for the CDC to transfer certain diagnostic technologies to state labs and, perhaps, additional labs. The CDC will house its own rapid-response and advanced technology (RRAT) lab, to respond at all times to the needs of any state or region. Analogous chemical laboratories will also be established.

In the area of response, the CDC is making a huge commitment. For a confirmed attack, the so called Presidential Decision Directive (PDD) 39 designates the FBI as the lead agency. For suspected attacks, the CDC will send out response teams to investigate the unconfirmed or suspicious illness.

The Communication System may be the most innovative of the directives. Indeed, by 2005 the CDC will implement a "state-of-the-art communication system to support surveillance," a "rapid notification and information exchange" of suspected bioterroristic outbreaks, rapid dissemination of diagnostic results, and finally an effective emergency response. Moreover, (and take note you hospital epidemiologists and front line ID physicians) the CDC will "provide terrorism-related training to epidemiologists. . .and other front line health care providers. . ." The piece of the proposal that seems most realistic is creation of a website to help with bioterrorism preparedness.

The next section, Partnerships and Implementation, lists all the groups who are involved in the grand scheme, and it is a daunting vision for sure. A set of priorities (Box 6) has been created for the years 2000-2002. The response priority includes establishment of a national pharmacy stockpile to offset biological and chemical agents.

COMMENT BY JOSEPH F. JOHN, MD

Well, this is as adventuresome an item as I have ever seen come out of the CDC. That is not to say it is not insightful, even needed, but the scope of these recommendations will take a level of national cooperation and commitment not seen since World War II. By their very nature, wars can command full commitment, but whether the spectre of bioterrorism can evoke the level of commitment, not to mention the financial support, necessary to pull off the grand scheme remains to be seen.

Financial and tactical support will certainly be welcomed at the regional and certain urban locations. We in New Jersey are already keenly aware of our strengths and weaknesses. Our State Department of Health already has a comprehensive plan that may be achievable in our small, though heavily populated, state. Still, it is hard enough to coordinate communication in any single state, including our state, so creating the type of "national electronic infrastsructure," that will prove effective to coordinate a national communication network poses a challenge on a much more complex level.

One of the most satisfying elements of the plan is the establishment of regional laboratories that will link to an around-the-clock suppot lab at the CDC that will "expedite molecular characterization of critical biological agents." Such a multilevel laboratory effort would certainly provide a net of protection that we currently lack. Such labs could also distinguish among emerging and reemerging pathogens that arise naturally from those that are purposely dispersed. I suspect that any highly multiresistant, emergent, nosocomial pathogen will be suspect and would have to be moved through the bioterrorism lab network.

Creation of new gene banks that include comprehensive databases of existing virulence genes and pathogenesis islands will help screen suspect microorganisms. A massive educational effort will be needed to coordinate regional labs and local labs with new gene banks. New personnel will need to be educated and the challenge of keeping the labs up to date will persist into the forseeable future.

My memory bank does not include a recollection of such an undertaking. My skeptical side chides about feasibility of certain recomendations, for example, like the scope implied by the wording of the last Recommendation: A cadre of well-trained health care and public health workers will be available in every state. I assume this means that the cadre is well trained and available to fight bioterrrorim. If that is the case, just how much is the government willing to spend on this project? From some cursory calculations, for a state like New Jersey, if we were to argue that at least one such person is needed for every million in population (I just pulled that ratio out of my hat), then that would require eight such individuals. The salary budget alone should approach $1 million for those individuals so that we start to approach real money when the entire nations falls under that type of extrapolation.

It is neither easy nor fun to write about bioterrorism. Have we really sunk so low as a species to have foisted this inevitability on ourselves? Doesn't the earth have enough problems without dredging up pathogenic microbes for homicidal means? Apparently not. Assuming we have sunk this low, and assuming that this massive national initiative has become necessary, then hats off to the innovators of this CDC document. They have covered the bases!

Ironically, just months after the publication of these guidelines, the *Morbidity and Mortality Weekly Report* itself reported an incident suspicious as a bioterroristic ploy.[1] Now, I must admit that I seldom think of a case of brucellosis as a potential terroristic event—but there you

are. New Hampshire (the Live Free or Die state) was the site of the suspicious incident. In March 1999, a woman was admitted to a New Hampshire hospital with an acute disease and paired sera on day 4 and 22 showed a 16-fold rise in titer for Brucella. Cultures of the blood were negative. The patient's family reported a possibility that the patient's boyfriend may have exposed her to laboratory flasks. The authorities got involved (this makes good reading) and, ultimately, there was no implication that this was biological terrorism.

Regarding the new CDC recommendations, let's see if the legislatures have the nerve to provide the support necessary. Hopefully we will never have to test our bioterrorism defenses, regardless of the state of their maturation. Yet, I suppose that the country will have to be convinced that our vulnerability is real before the upper levels of the CDC recommendations can be realized. In the interim, physicians, in particular our infectious disease and public health physicians, need to lead the preparedness effort and understand how the pathogens they have studied well may manifest in a biological attack. ❖

Reference

1. Suspected brucellosis case prompts investigation of possible bioterrorism-related activity—New Hampshire and Massachusetts, 1999. *MMWR Morb Mortal Wkly Rep* 2000;49:509-512.

Cigarette Smoking and Invasive Pneumococcal Disease

ABSTRACT & COMMENTARY

Synopsis: *Cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults.*

Source: Nuorti JP, et al. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.

The highest incidence of invasive pneumococcal disease is found among young children and the elderly. The highest absolute number of infections, however, is found in nonelderly adults. Although some may have predisposing risk factors (e.g., chronic illness), many adults with invasive pneumococcal disease do not have any recognizable risk factors. The contribution of cigarette smoking to the risk of invasive pneumococcal disease is unclear though approximately half of otherwise healthy adults with invasive pneumococcal disease are cigarette smokers.

To assess the contribution of active and passive smoke to the risk of invasive pneumococcal disease, Nuorti and associates designed a population-based case-control study. This study targeted immunocompetent nonelderly adults between 18 and 64 years of age. They included only community-acquired cases of invasive pneumococcal disease, which was defined as an illness in which *Streptococcus pneumoniae* was isolated from a normally sterile site, such as blood or cerebrospinal fluid. Immunocompromised, immunosuppressed, and institutionalized patients were excluded. Chronic illness was present in 23%, and 28% had an indication for the pneumococcal vaccine, of which only 9% actually received the vaccine.

Among those with invasive pneumococcal disease, 57% of men, 59% of women, 64% of nonblacks, and 51% of blacks were current smokers. Among the controls, 26% of men, 26% of women, 25% of nonblacks, and 24% of blacks were current smokers. There were an equal percentage of patients and controls in both groups who were former smokers, but the average time patients had quit smoking was 11.3 years while controls had quit for an average of 17.0 years. Patients were 4.1 times as likely as controls to be current smokers. Further, a linear dose-dependent relationship was found with higher risk with increasing pack-years of smoking. Finally, for former smokers, the risk of invasive pneumococcal disease declined with increasing time since quitting.

Among nonsmokers, 33% of patients and 17% of controls were exposed to passive smoke. Those exposed to passive smoke were 2.5 times as likely to develop invasive pneumococcal disease. Individual chronic diseases (e.g., COPD, diabetes, and heart failure) did not increase the risk for invasive pneumococcal disease, but when classified as chronic illness collectively, these patients were 3.3 times as likely to develop disease. Other factors associated with invasive pneumococcal disease included living with children younger than 6 years of age who attended daycare, low socioeconomic status, male sex, black race, and low level of education.

This article examines the risk factors that can be associated with pneumococcal disease. Although multiple factors are associated with increased risk for *S. pneumoniae* infection, Nuorti et al conclude that cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease in immunocompetent, nonelderly adults.

COMMENT BY DAVID OST, MD

One of the many health consequences of cigarette

smoking is acute respiratory tract infection.[1] Smoking increases the risk for community-acquired pneumonia.[2] This risk is also present in the immunocompromised host, such as those infected by HIV.[3] The pathophysiologic effects include: 1) alterations of central airways with loss of cilia and mucus gland hyperplasia; 2) alterations of peripheral airways with inflammation, goblet cell metaplasia, and mucus plugging; 3) alterations of alveoli and capillaries with elevated numbers of activated inflammatory cells and destruction of peribronchiolar alveoli; and 4) alterations of immune function with reduced immune response to inhaled antigens.[1]

This study has important implications for the practice recommendations of the pneumococcal vaccine and benefits of smoking cessation. The pneumococcal vaccine is recommended for the elderly and those with chronic illnesses; this study suggests that it may be beneficial in smokers as well. The plausibility and cost-effectiveness of such strategies need to be evaluated. (*Dr. Ost is Director of Interventional Pulmonology, Northshore University Hospital, Manhasset, NY.*) ❖

References

1. Sherman CB. *Med Clinics North Am* 1992;76:355-375.
2. Almirall J, et al. *Chest* 1999;116:375-379.
3. Conley LJ, et al. *AIDS* 1996;10:1121-1126.

Rabies Postexposure Prophylaxis

ABSTRACT & COMMENTARY

Source: Moran GJ, et al. Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. *JAMA* 2000;284:1001-1007.

In that there has been but a single confirmed rabies survivor in the United States in the last three decades, rabies may be acknowledged as a uniformly fatal disease. Thanks primarily to control of rabies in domestic animals, the number of annual cases has dropped from more than 100 at the beginning of the 20th century, to only 1-3 yearly.

Rabies among animals, however, especially raccoons, has increased almost 20% since 1996. No cases of human rabies have ever been documented subsequent to exposure to raccoon rabies. Appropriate administration of rabies prophylaxis treatment is important not only to prevent rabies, but also to avoid unnecessary administration to persons not at risk, since the process is not without discomfort, and is costly ($1500 for a treatment course alone, without physician or office/hospital fees). This trial is the first prospective one to assess appropriateness of rabies prophylaxis administration.

Of 2030 patients with rabies exposure, 6.7% received prophylaxis. Of 136 patients who received prophylaxis, 40% were considered inappropriate, most commonly due to the fact that the culprit animal was available for observation or testing, which could obviate intervention. Of 1894 persons not receiving prophylaxis, 6.3% were considered inappropriate, most commonly because the culprit animal was not available for observation.

Moran and colleagues conclude that enhanced adherence to appropriate use of rabies prophylaxis is needed, and may be advanced by provision of easy access to and availability of suggested locale-specific and circumstance-specific guidance, through health department assistance and guideline promulgation. (*Dr. Kuritzky is Clinical Assistant Professor, University of Florida, Gainesville, Fla.*) ❖

CME Questions

21. A new set of CDC recommendations for bioterrorism preparedness advises all of the following *except*:
- a. extended research on antiviral drugs and vaccines.
- b. stockpile appropriate vaccines and drugs.
- c. deploy foreign nationals trained in bioterrorism to our state capitals to act as intelligence agents.
- d. establish a national communications network to facilitate dissemination of information about bioterrorism events.

22. What is the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults?
- a. Chronic obstructive pulmonary disease
- b. Congestive heart failure
- c. Cigarette smoking
- d. Low socioeconomic status

23. Which one of the following is correct?
- a. Ebola virus infection is mosquito-borne.
- b. The endemic reservoir of Rift Valley Fever virus is small rodents.
- c. Ebola virus is endemic in ruminants.
- d. Ebola virus can be transmitted from human to human.

In Future Issues:

Corticosteroid Treatment for Septic Shock: New Insights