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Mosquito Repellents: What Works?

ABSTRACT & COMMENTARY

Synopsis: *The efficacy of several commercially available insect repellents was compared. The topical application of compounds containing DEET was far more protective against mosquito bites than was application of products containing soybean oil or citronella. With the resurgence of West Nile virus in the southern United States this summer, and the potential for spread of infections, mosquito protection assumes even greater relevance at this time.*

Source: Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med.* 2002;347:13-18.

IN A LABORATORY SETTING, ADULT LABORATORY WORKERS EXPOSED AN ARM to caged, hungry female *Aedes* mosquitoes while using a variety of commercially available insect repellents. Sixteen separate repellent formulations were evaluated in a total of 270 test episodes on the 15 volunteer subjects. The time elapsed until the first bite was noted as the end point of “complete protection time.”

The Table highlights a few of the relevant results. Topically applied products were generally more effective than were impregnated wristbands. DEET-containing products varied in efficacy with longer protection noted with higher concentration formulations. Citronella-containing products provided less than half an hour of protection.

■ COMMENT BY PHILIP R. FISCHER, MD, DTM&H

Travel medicine practitioners are well aware of the importance of insect repellents in preventing mosquito-transmitted infections such as malaria, yellow fever, and Japanese encephalitis. In addition, the use of insect repellents is also protective against many tick-borne diseases. With the westward and southward expansion of the endemic region of West Nile virus in North America, even nontravelers are increasingly interested in avoiding insect bites.

Advertisements, anecdotes, and the lay literature include many claims about the effectiveness and safety of various insect repellents. Fradin and Day, in a recent issue of the *New England Journal of Medicine*, have provided practically useful information about the relative efficacy of various readily available repellents.

For approximately 4 decades, DEET (also known as N, N-diethyl-metoluamide or N, N-diethyl-3-methylbenzamide) has been the most widely used

Table
Protective Efficacy of Various Insect Repellents

Product	Active Ingredient	Mean Complete Protection Time (min)
OFF! Deep Woods	DEET, 23.8%	302
Sawyer Controlled Release	DEET, 20%	234
OFF! Skintastic	DEET, 6.65%	112
Bite Blocker for Kids	Soybean Oil, 2%	95
OFF! Skintastic for Kids	DEET, 4.75%	88
Skin-So-Soft Bug Guard Plus	IR3535, 7.5%	23
Natrapel	Citronella, 10%	20
Skin-So-Soft Bug Guard	Citronella, 0.1%	10
Skin-So-Soft Moisturizing Suncare	Citronella, 0.05%	3
Various wristbands	DEET or Citronella	< 0.5

Adapted from: N Engl J Med. 2002;347:16.

insect repellent.¹ With questions about the safety of DEET for human usage, alternative products have been developed. Fradin and Day have now clearly shown that DEET-containing repellents are markedly more effective than other common repellent preparations. Under standardized conditions, DEET protected against mosquito bites for much longer than any of the other preparations. As suggested in previous studies, the duration of DEET's protection depends on the DEET concentration; peak protection is conferred by products containing about 30% DEET. Though not specifically studied in this investigation, it is not clear that high concentrations of DEET (such as the 90+% products available in some camping stores) are more effective than products containing "only" 20-30% DEET. Interestingly, a "long-acting" formulation of DEET did not seem to protect for any longer than a similarly concentrated standard formulation. Botanical preparations containing citronella protected only for a few brief minutes. Of note, repellents were not significantly protective when applied only to a nearby wristband. The message should be clear to travelers and to domestic residents at risk of exposure to mosquitoes carrying disease: **DEET is the most effective mosquito repellent.**

But, is laboratory testing using caged *Aedes* mosquitoes relevant to the conditions faced by travelers? It is impossible to perfectly replicate any individual traveler's situation in an artificial environment. Different individuals are differentially attractive to mosquitoes [with pregnant women being particularly appealing²], and insect repellents are not always applied in a completely careful manner. Repellent efficacy varies somewhat between different genera and species of mosquitoes as well. These

factors should make us cautious about guaranteeing any specific repellent's duration of protection for a particular traveler, but the relative efficacy for the different products tested would not be expected to change between individuals and settings.

What about safety? When ingested, DEET can have neurotoxic effects. It can also cause irritation when rubbed into eyes or, in some individuals, when rubbed vigorously (such as in elbow creases) on the skin in high concentrations. Clearly, oral and ocular applications of DEET (such as can occur inadvertently in children who rub their faces with DEET-laden hands or lick their DEET-treated forearms) should be avoided.

However, there have been a few, albeit rare, reports of serious and even fatal episodes in children who used DEET. In those cases, inappropriately frequent application (up to 10 times in a day) and oral ingestion (licking of arms) were sometimes reported, and there is no good evidence linking DEET concentration to the risk of toxicity. Of course, no product is perfectly safe. Citronella toxicity has also been reported.³

Since 1998, the American Environmental Protection Agency has removed restrictions on the concentration of DEET used in children. The American Academy of Pediatrics has acknowledged that lower concentrations of DEET are not safer than higher concentrations and that higher concentrations of DEET are more effective in repelling insects than are formulations with lower concentrations.⁴ Each organization does stress the importance of *appropriate* use of DEET with care: 1) not to apply the repellent on or near the eyes or mouth; 2) to apply the repellent only on exposed skin (not skin covered by clothes); and 3) to wash remaining DEET off the skin when leaving an area of risk for insect bites. In Canada, where recent safety concerns have limited DEET concentrations, the use of products containing up to 30% DEET is still accepted and advocated.

The editorial accompanying the report by Fradin and Day⁵ wisely summarizes DEET safety when writing that DEET is far less toxic than many people believe. Adverse effects, though documented, are infrequent and are generally associated with gross overuse of the product. The risk of DEET-related adverse effects pales in comparison with the risk of acquiring vector-borne infection in places where such diseases are endemic.

This summer, Fradin and Day have provided a great service though their *New England Journal of Medicine* paper. Their solidly scientific study reminds us that DEET-containing insect repellents are much more effective than other products and that DEET efficacy increases with increasing DEET concentration. Appropriate use of DEET, both at home and in travelers, should result in improved health for many people. ■

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Tularemia as Terror

ABSTRACT & COMMENTARY

Synopsis: *Tularemia is a bacterial zoonosis caused by one of the most infectious pathogenic bacteria currently known, Francisella tularensis. Inhalation or inoculation of as few as 10 organisms can cause disease. F tularensis has previously been considered a potent agent for bioterrorism. Given recent bioterrorist events, this review highlights known disease manifestations, as well as unusual patterns of disease occurrence and summarizes reports of known cases occurring in the United States between 1990 to 2000.*

Source: Tularemia—United States, 1990-2000. *Morb Mortal Wkly Rep MMWR.* 2002;51:181-184.

IN 1911, TULAREMIA WAS FIRST DESCRIBED AS A plague-like disease of rodents, but it was soon recognized as a serious and sometimes fatal illness of humans, who are infected through various unique environmental exposures. Large waterborne outbreaks occurred in Europe and the Soviet Union in the 1930s and 1940s, which demonstrated the organisms' epidemic potential. The highest incidence of human cases in the United States occurred in 1939 and through the 1940s—mostly as a result of infective arthropod bites, or from hunters handling animal tissues, such as rabbit skins.

F tularensis can be found in widely diverse animal hosts and habitats where natural reservoirs of infection persist in small mammals such as voles, mice, water rats, squirrels, and rabbits, which acquire their infections through bites by ticks, flies, and mosquitoes or by contact with contaminated water soil or vegetation. Lawn mowing or brush cutting has also been associated with outbreaks of tularemia in the United States. Persons of all ages and both sexes appear to be equally susceptible, although activities such as hunting, trapping, butchering and farming have been traditionally most likely to cause exposures in adult men. The organism represents a truly virulent laboratory hazard as workers can accidentally inoculate themselves or inhale aerosolized organisms.

Though highly infectious, person-to-person transmission has not been documented.

The incidence of tularemia in the United States has declined substantially since the first half of the 1900s. The number of cases has continued to decline since the 1950s. Recent cases are clustered, as seen in the Figure, within Arkansas, Missouri, South Dakota, and Oklahoma accounting for the majority of reported cases. From 1990 to 2000, a total of 1368 cases of tularemia were reported to the CDC. Fifty-nine percent were reported as confirmed and 6% were reported as probable. The disease was not classified as a notifiable disease from 1995 to 1999 but an increase in reporting occurred during 2000 when notifiable status was restored. Annual incidence was highest in persons aged 5-9 years and in persons older than 75 years. Males had a higher incidence in all age categories. Incidence was highest among American Indians/Alaska Natives, compared with whites, blacks, and Asian/Pacific Islanders. Date of onset was available in 936 cases—of which 70% reported onset during May through August, although cases were reported during all months of the year.

Tularemia characteristically presents as an acute febrile illness typically associated with fatigue, chills, headache, body aches, and malaise. *F tularensis* is a facultative intracellular bacterium that multiplies within macrophages. The major target organs are lymph nodes, lungs and pleura, spleen, liver, and kidneys. Depending upon route of infection, various clinical manifestations can include granulomatous ulceration at the site of cutaneous or mucous membrane inoculation, pharyngitis, ocular lesions, regional lymphadenopathy, and pneumonia. (See Table 1.) During the largest recorded airborne tularemia outbreak in 1966, which occurred in a farming area of Sweden, 10% of confirmed patients had symptoms of pneumonia such as dyspnea and chest pains.

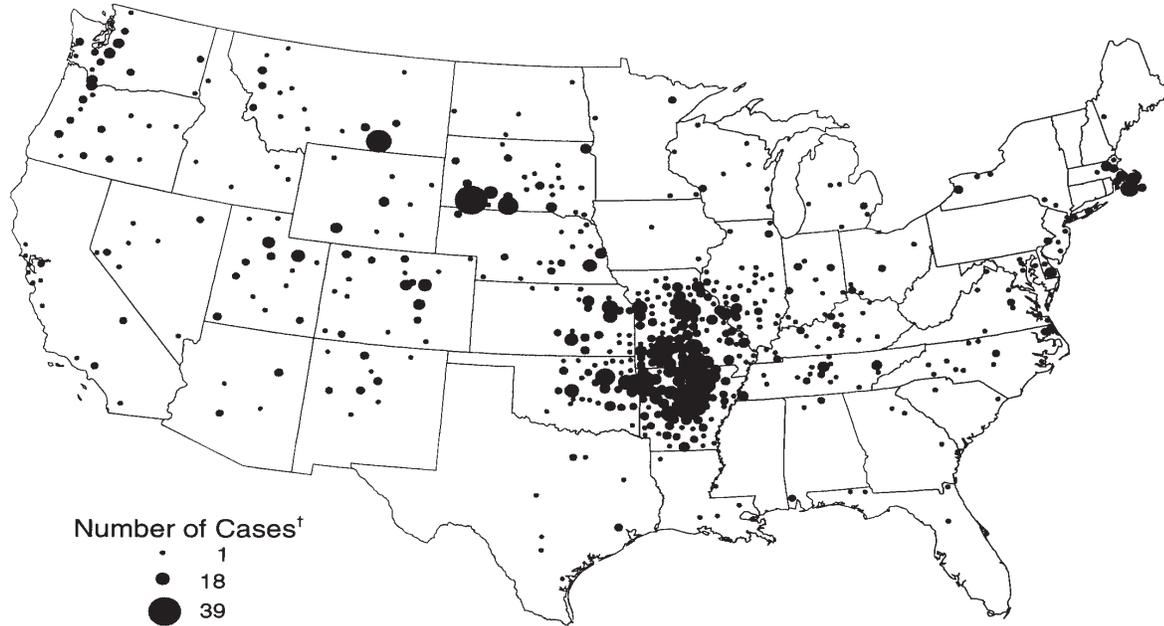
Any form of tularemia may be complicated by hematogenous spread resulting in secondary pleuropneumonia, sepsis, and rarely meningitis.

Typhoidal tularemia is a term used to describe illness in persons with fever and constitutional signs without cutaneous or mucosal involvement. Sometimes these patients present with prominent gastrointestinal manifestations, such as diarrhea and pain. Tularemia sepsis is potentially severe and fatal, and presents with an initial nonspecific intestinal syndrome followed soon after by a toxic appearance, confusion, coma, shock, DIC, ARDS, and multiorgan failure.

In ulceroglandular tularemia, the form that typically arises from handling a contaminated carcass or following an infective bite, a local cutaneous papule appears at the inoculation site at about the time of onset of generalized

Figure

Reported Cases* of Tularemia—United States, 1990-2000



* Based on 1347 patients reporting county of residence in the lower continental United States. Alaska reported 10 cases in four counties during 1990-2000.

† Circle size is proportional to the number of cases, ranging from 1-39.

Adapted from: *Morb Mortal Wkly Rep MMWR*. 2002;51:183.

symptoms. It becomes pustular and ulcerates within a few days of its first appearance. The ulcer is tender, indolent and may be covered by an eschar. Typically, one or more regional lymph nodes may become enlarged and tender within days, and may rupture even with antibiotic treatment. Oculoglandular tularemia follows direct contamination of the eye with ulceration of the conjunctiva as well as chemosis, vasculitis, and regional lymphadenitis. The glandular form is characterized by lymphadenopathy without an ulcer. Oropharyngeal tularemia is acquired by drinking contaminated water ingesting contaminated food, or by inhaling contaminated droplets or aerosols. Stomatitis, exudative pharyngitis or tonsillitis with ulceration can occur. Pronounced cervical or retropharyngeal lymphadenopathy can occur.

Presumptive diagnosis of tularemia can be made by direct fluorescent antibody or immunohistochemical stains of secretions, exudates, or biopsy specimens. By light microscopy the organism is characterized by its small size (0.2 μm \times 0.2-0.7 μm) pleomorphism and faint staining. It is easily distinguished from the plague organism (*Yersinia pestis*), which shows bipolar staining, and from anthrax (*Bacillus anthracis*), which is a large gram-positive rod. Definitive diagnosis is by culture of the organism or by a fourfold titer change of serum antibodies against *F tularensis*.

Table

Diagnosis of Inhalational Tularemia Following Use of a Biological Weapon¹

Clinical Findings

Sudden onset of acute febrile illness, progressing in some patients to pharyngitis, bronchiolitis, pneumonitis, pleuritis, hilar lymphadenitis; May lead to sepsis and inflammatory response syndrome.

Epidemiology

Point-source outbreak pattern; likely urban. Unexpected severe respiratory illness in otherwise healthy persons.

Microbiology

Small, Gram-negative coccobacilli in direct stain of respiratory secretions. Sputum, tracheobronchial secretions, and blood should be cultured using cysteine-enriched medium. Antimicrobial susceptibility of isolates should be determined. Direct fluorescent antibody stain is first-line, rapid-identification procedure at reference laboratories. Polymerase chain reaction and antigen detection procedures may also provide rapid identification. Microagglutination assay can detect serum antibodies beginning 10 days after illness onset.

Pathology

Histological findings of acute suppurative necrosis followed by granulomatous reactions.

Radiology

Peribronchial infiltrates leading to bronchopneumonia in 1 or more lobes, often accompanied by pleural effusion and enlarged hilar nodes.

■ COMMENT BY MARIA D. MILENO, MD

The incidence of tularemia in the United States remains low following a dramatic decline in the second half of the 20th century. A weapon using airborne tularemia would likely result in pulmonary presentations 3-5 days later, such as an outbreak of an acute febrile illness with ensuing pneumonia, pleuritis, and hilar adenopathy. Unusual clustering of such cases should lead to early suspicion of intentional tularemia. Until an etiology is clearly established, clinicians would need to work closely with epidemiologists and diagnostic laboratories to differentiate the illness from various community-acquired pneumonias and to exclude other bioterrorist weapons such as those causing plague, anthrax, or Q fever. Prompt treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin is recommended while awaiting laboratory confirmation. Without treatment the clinical course could progress rapidly to respiratory failure, shock, and death. Treatment with aminoglycosides should be continued for 10 days. Exposed persons should be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin. ■

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Outbreak of *Mycobacterium tuberculosis* in African Mongooses and Meerkats: What, Me Worry?

ABSTRACT & COMMENTARY

Synopsis: *Mycobacterium tuberculosis* causes an outbreak of disease and death in free-ranging wildlife in Botswana and South Africa. Why should this be of concern to practitioners of travel medicine and their patients?

Source: Alexander, KA et al. *Mycobacterium tuberculosis*: An emerging disease in free-ranging wildlife. *Emerg Infect Dis*. 2002;8:598-601.

ALEXANDER AND COLLEAGUES REPORT AN OUTBREAK of *Mycobacterium tuberculosis* in free-ranging banded mongooses (*Mungos mungo*) and suricates (*Suricata suricatta*). Suricates are small, burrowing mammals more familiarly known as meerkats.

Behavioral ecologists began monitoring 12 troops of meerkats along the dry bed of the Kuruman River in South Africa from October 1998 to December 1999. This epizootic began when an unknown infected male meerkat with enlarged cervical lymph nodes joined the study group of 5 adults and 15 pups. A month later, the lymph nodes of the infected animal ruptured and began draining pus, eventually becoming a persistent nonhealing wound. Progressive cachexia and debilitation occurred until the animal eventually disappeared. Within 2 months, signs of disease such as lymphadenopathy, weakness, and emaciation appeared among other animals in the group. Eventually all members of the troop either died, disappeared (presumed dead), or were euthanized. One human case of tuberculosis (TB) was known to have occurred in the vicinity of the meerkat burrows. The affected animals were seen foraging around roads and "investigating" human sputum.

Another group of scientists identified an epizootic in banded mongooses at the northern extreme of Chobe National Park in Botswana from June to September 1999. Disease spread quickly to 6 different troops. The last case occurred in September 1999. No new cases appeared during monitoring through January 2001. Human garbage pits and a human TB case were near the initial outbreak sites. Banded mongooses were seen feeding regularly at these garbage pits.

Gross postmortem examination of the animals (1 meerkat, 7 mongooses) revealed lymphadenopathy and miliary masses in various organs including liver, spleen, lungs, and kidneys. Histopathologic examination showed granulomas in many organs as well as acid-fast organisms in the cytoplasm of macrophages.

Specimens from 1 mongoose and 1 meerkat grew acid-fast colonies on Lowenstein-Jensen media after 5-6 weeks. The isolates produced niacin and reduced nitrates, characteristics that are typical of *M tuberculosis*. *Mycobacterium bovis* is usually niacin-negative and does not reduce nitrates. In addition, these specimens were PCR amplified using a protocol of de Witt et al to differentiate *M tuberculosis* from *M bovis*.¹ Findings were consistent with *M tuberculosis*.

■ COMMENT BY MARY-LOUISE SCULLY, MD

Humans are the only reservoir for *M tuberculosis* whereas *M bovis* is widespread in domestic, captive and free-ranging wildlife populations.² Previous reports have shown possible transmission of *M tuberculosis* in situations of captivity or close, prolonged contact between animals and humans, such as the 4 elephants and their trainer at an exotic animal farm in Illinois in 1996. The DNA fingerprint comparisons showed that the isolates were the same strain, suggesting transmission of *M*

tuberculosis between humans and elephants.³

These epizootics reported in mongooses and meerkats occurred in the vicinity of human cases of TB though no further details on the human cases are available. The researchers suspected transmission occurred via an oral route via animal exposure to human excretions and secretions in the surrounding environment. An increase in these exposures seems inevitable. In 1999 alone, more than 89,000 visitors to Chobe National Park were recorded.⁴

Death and disease due to TB continue to increase, especially in developing countries where HIV is prevalent as well. In Botswana, the TB infection rate increased from 202 per 100,000 in 1989 to 537 per 100,000 in 1999. In addition, 36% of women receiving routine antenatal care in Botswana in 1999 were seropositive for HIV.⁵ Coexisting HIV and TB can influence the severity of TB infection and shorten the time from initial TB infection to development of overt disease, potentially increasing the amount of TB shed into the environment. Some evidence suggests that concurrent helminthic infections may decrease the host immune response to TB, further increasing the burden of TB in Africa and developing countries.⁶

Transmission of human disease to animals is not new, although public attention is often more focused on the reverse situation. In 1998, evidence strongly linked the death of 6 endangered mountain gorillas in Rwanda to human measles. The epidemic was abruptly stopped by the administration of measles vaccine to the remaining 65 healthy gorillas.⁷ As humans and animals share the world's dwindling resources and habitats, more disease overlap will invariably occur. Even more unsettling is whether these infected animals could become new reservoirs for pathogens previously confined to humans. Clearly this would pose a new challenge in the attempt at TB and other disease eradication. ■

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Rickettsialpox in North Carolina

ABSTRACTS & COMMENTARY

Synopsis: This study reports the first case of rickettsialpox in southern United States caused by infection with *R. akari*. The North American range for rickettsial disease expands even as newer agents are discovered abroad.

Sources: Krusell A, et al. Rickettsialpox in North Carolina: A case report. *Emerg Infect Dis.* 2002;8(7):727-728; Kelly D, et al. The past and present threat of rickettsial diseases to military medicine and international public health. *Clin Infect Dis.* 2002;34(Suppl 4):S145-S169.

A 48-YEAR-OLD MAN WHO HAD WORKED AT A GOLF course was admitted with fevers, chills, severe headache and a rash. Seven days prior to admission he had felt an insect bite that developed into an ulcerated papule. Two days before admission, red macules appeared over his anterior chest and then became vesicular.

The patient had a pet dog and cat but had not traveled outside North Carolina in the 3 months before admission. He did notice his cat had brought dead mice to his grounds but he never directly touched them. He reported no recent tick exposures or insect bites. On admission the patient appeared ill, was febrile, and had an eschar on his posterior right thigh. A macular vesicular rash was present on his trunk, arms and legs. All lab values were normal except his low platelet count of 85,000/ μ l. A clinical diagnosis of rickettsialpox was made and he was treated with doxycycline and cefazolin. He defervesced within 48 hours.

Two serum samples were submitted to CDC, Atlanta. Samples were tested by a standard IFA for IgG antibodies reactive with *Rickettsia akari* and *R. rickettsii* antigens. Because of antibody cross-reactivity among the spotted fever group organisms, confirmatory cross-adsorption testing was performed and it confirmed *R. akari* (rickettsialpox) infection.

Table Principle Causative Agents, Modes of Transmission, and Distribution of the Rickettsial Diseases of Military Importance			
Group, disease	Causative agent	Mode of transmission	Geographic distribution
Typhus			
Epidemic typhus	<i>Rickettsia prowazekii</i>	Infected human body louse feces; flying squirrel flea	Worldwide
Brill-Zinsser disease	<i>R. prowazekii</i>	Recrudescence of latent <i>R. prowazekii</i> infection	Worldwide
Murine (endemic) typhus	<i>Rickettsia typhi (mooseri)</i>	Infected rat flea feces	Worldwide
Spotted fever			
Rocky Mountain spotted fever, Brazilian spotted fever	<i>Rickettsia rickettsii</i>	Tick bite	North and South America
Boutonneuse fever, Mediterranean spotted fever	<i>Rickettsia conorii</i>	Tick bite	Mediterranean littoral to India, Africa
Astrakhan spotted fever	<i>Rickettsia caspii</i>	Tick bite	Astrakhan, Russia
North Asian (Siberian) tick typhus	<i>Rickettsia sibirica</i>	Tick bite	Siberia, Armenia, Pakistan, northern China
Oriental (Japanese) spotted fever	<i>Rickettsia japonica</i>	Tick bite	Southwest Japan
Australian (Queensland) tick typhus	<i>Rickettsia australis</i>	Tick bite	Queensland, Australia
African tick bite fever	<i>Rickettsia africae</i>	Tick bite	Sub-Saharan Africa
Israeli tick typhus	<i>Rickettsia sharonii</i>	Tick bite	Israel
Rickettsialpox	<i>Rickettsia akari</i>	Mite bite	USA, Korea, Ukraine, Croatia
Flinders Island tick typhus	<i>Rickettsia honei</i>	Tick bite	Flinders Island, Tasmania
Asian or thai tick typhus	<i>TT-118</i>	Tick bite	Thailand, Malaysia
Cat flea typhus	<i>Rickettsia felis</i>	Cat flea bite (?)	Western and southwestern USA
Scrub typhus	<i>Orientia tsutsugamushi</i> ^a	Chigger bite	Afghanistan, Pakistan, and India to Siberia, Southwest Pacific Islands, Southeast Asia, northern Australia
Ehrlichioses ^b			
Canine ehrlichiosis; tropical canine pancytopenia	<i>Ehrlichia canis</i>	Tick bite	Southeast Asia, southwestern USA, Venezuela
Human monocytic ehrlichiosis	<i>Ehrlichia chaffeensis</i>	Tick bite	Americas, Europe, Thailand
Human granulocytic ehrlichiosis	<i>Anaplasma phagocytophila</i>	Tick bite	USA, Europe
Sennetsu fever	<i>Neorickettsia sennetsu</i>	Unknown	Japan, possibly Malaysia
Q fever	<i>Coxiella burnetii</i>	Infectious aerosol, tick bite	Worldwide
Bartonellosis ^c			
Trench fever	<i>Bartonella quintana</i>	Infected louse feces into skin; rodent contact (?)	USA, Mexico, Europe, Africa, Middle East, China, Japan, Bolivia
Bartonellosis (Oroya fever, Verruga peruana, Carrion's disease)	<i>Bartonella bacilliformis</i>	Infected sand fly	Andes Mountains of Colombia, Ecuador, Peru, 610-2440 m elevation
Cat scratch disease	<i>Bartonella henselae</i>	Cat or dog contact	North America, Europe
Bacillary angiomatosis	<i>Bartonella species</i>	Unknown	Worldwide
Rodent bartonellosis	<i>Bartonella elizabethae</i> , <i>Bartonella species</i>	Rattus or other rodent contact	Worldwide

Table continued on page 32

■ COMMENT BY MICHELE BARRY, MD, FACP

This patient had a classic clinical presentation for *R. akari* infection with an eschar, vesicular rash, thrombocytopenia, and severe headache. Fever and vesicular rash can sometimes cause confusion with chickenpox or other viral exanthems. However, the presence of an eschar at the site of inoculation and the lack of successive crops of vesicles over time should distinguish the rash from varicella and alert clinicians to the possibility of rickettsialpox.

R. akari is transmitted from mice to humans by the house mouse mite. Rickettsialpox was first described in humans in 1946 in a group of residents in apartments clustered within a 3-block area of Queens, NY! Most cases to date have occurred in large metropolitan areas of the northeastern United States. Morbidity and mortality caused by rickettsioses have had a major influence on military activities and public health for > 2000 years. The military experience with epidemic rickettsialpox has been recently described in a *Clinical Infectious Disease* supplement. The diseases caused by these organisms are notoriously difficult to diagnose because they share symptoms with many other febrile diseases with similar epidemiology.

The rickettsioses, historically included the families of Rickettsiaceae, Bartonellaceae and Anaplasmataceae. (see Table.) They were originally defined as obligate

intracellular parasites that grew only within eukaryotic host cells. Members of the family Bartonellaceae have been removed from this family as they grow fastidiously on enriched culture media and share different DNA/RNA sequences. In the past, human rickettsial diseases caused by members of the genus *Rickettsia* were collectively called "typhus fever." Later the typhus fevers were differentiated by a characteristic lesion (eg, the eschar of scrub typhus), causative agent or vector (eg, louse, flea, tick,

Table continued

- ^a *Rickettsia tsutsugamushi* was renamed *Orientia tsutsugamushi* because of differences > 10% in 16S rRNA and in cell wall structures that lack lipopolysaccharide and peptidoglycan typical of other members of the genus.
- ^b Molecular phylogenetic analyses with use of 16S rRNA gene and groESL operon nucleic acid data and serological cross-reactions suggest that current species of genus *Ehrlichia* should be distributed into genera of the Anaplasmataceae, which are now designated as *Ehrlichia*, *Anaplasma*, *Neorickettsia*, and *Wolbachia*. *Ehrlichia sennetsu* is now designated *Neorickettsia sennetsu*.
- ^c 16S rRNA sequence data, DNA relatedness data, guanine-plus-cytosine content, and other phenotypic characteristics have resulted in unification of genera *Bartonella* and *Rochalimaea*, and proposed removal of family Bartonellaceae from order Rickettsiales.

mite). Although all agents caused somewhat similar clinical syndromes, characterization of the causative agents resulted in 3 distinct groupings: spotted fever rickettsiosis; typhus (louse-borne epidemic typhus, murine or endemic typhus); and scrub typhus group.

Diagnosis

Early in the 20th century the nonspecific Weil-Felix serological test using *Proteus* species bacterial antigens was used to diagnose typhus and spotted fever rickettsial disease and modified for diagnosis of the scrub typhus group. Although lacking specificity (66%) and sensitivity (80%), the Weil-Felix test has been inexpensive and commercially available to developing countries. The IFA test was developed in the 1960s and is used as a reference standard for more developed countries. Recently PCR has become available in advanced clinical labs.

Prevention and Bioterrorism

As rickettsial agents are inexpensively and easily mass produced, they are considered select agents for a potential bioterrorism threat. The US military currently has limited capability to prevent rickettsial diseases. There are no FDA-licensed vaccines for protection although there is evidence that weekly doxycycline prophylaxis can reduce morbidity. DDT used effectively during WWII to control louse-borne typhus is no longer legal to use in the United States, but DEET and permethrin treated uniforms can effectively reduce the risk of chigger, tick and flea-borne transmission of rickettsial diseases. ■

CME Questions

13. Insect repellents containing 20-30% DEET are:

- a. dangerous in young children, due to excessive absorption through skin.
- b. more effective than citronella-containing repellents.
- c. equally effective as repellents containing 10% citronella for mosquitoes.
- d. clearly useful when applied only to wristbands in attempts to avoid toxicity.

14. Which of the following statements about tularemia is true?

- a. *Francisella tularensis* is a poor agent for potential bioterrorism because of its low infectivity.
- b. Tularemia occurs throughout much of North America and Eurasia.
- c. Only a few small mammals are capable of maintaining tularemia in their populations.
- d. Bioterrorism with the agent of tularemia is most likely to be manifest as unexplained neurological infection in young adults.
- e. Neither doxycycline nor ciprofloxacin can be used effectively for prophylactic treatment of tularemia

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PHARMACOLOGY WATCH



No Shortage in Sight for Tetanus-Diphtheria Vaccine

The number of vaccine shortages has been unprecedented in the last year, but at least one vaccine, tetanus-diphtheria (Td), is back in full production. The Centers for Disease Control and Prevention (CDC) has announced that they are removing restrictions on the Td booster. Despite the fact that there is only one manufacturer of the vaccine, supplies are large enough to resume routine vaccination. The news is also good for childhood vaccines that have been in short supply, including MMR, varicella, and PCV-7 (pneumococcal) vaccine. All are expected to be in full supply by the end of the year.

Cholesterol-Lowering Therapy OK for Seniors

What to do with the 75-year-old patient with a cholesterol of 300, but no history of heart disease? Primary prevention studies have shown a benefit for treatment of younger patients, but there have been few studies of primary prevention studies in the elderly. Now data from the Cardiovascular Health Study of patients age 65 or older suggest that cholesterol-lowering therapy is useful in older patients as well. After nearly 7.5 years of follow-up, elderly patients with elevated cholesterol levels clearly benefited from cholesterol-lowering treatment. Compared with no drug therapy, statin use was associated with a decreased risk of cardiovascular events (multivariate hazard ratio [HR], 0.44; 95% CI, 0.27-0.71) and all-cause mortality (HR, 0.56; 95% CI, 0.36-0.8). This translates into a relative risk reduction of 56% of incident cardiovascular events and a 44% reduction in all-cause mortality. This was a prospective study, as pointed out in an accompanying editorial; however, it does add to the body of medical literature that suggests that the recent National Cholesterol Education Program (NCEP) guidelines should apply to those aged 65 or older (*Arch Intern Med.* 2002;162:1395-1400; editorial 1329-1331).

Beta-Blockers and CABG Patients

Preoperative beta-blockers have been shown to reduce operative complications and mortality in noncardiac surgery, and now 2 studies confirm the importance of beta blockade in patients undergoing coronary artery bypass grafting (CABG). In a large observational analysis of more than 600,000 patients undergoing CABG, preoperative beta-blocker therapy was associated with a small but consistent survival benefit in all patients except those with a preoperative left ventricular ejection fraction of less than 30% (*JAMA.* 2002;287:2221-2227). The most common postoperative complication of CABG is atrial fibrillation. A recent meta-analysis compares beta-blockers, sotalol, amiodarone, and biatrial pacing to prevent atrial fibrillation after heart surgery. All 4 modalities were effective (odds ratio compared to placebo—beta-blockers 0.39, sotalol 0.35, amiodarone 0.48, biatrial pacing 0.46). Each of the 4 drug modalities also significantly reduced length of stay. Significantly, beta-blockers, which are safe and easily administered were as effective as other treatment modalities (*Circulation.* 2002;106:75-80).

Asthma Sufferers: Use Clarithromycin

Asthmatics with evidence of infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* ben-

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efit from a 6-week course of the macrolide antibiotic clarithromycin, according to a new study. In 55 patients with stable asthma in the Denver community, 31 were found to have evidence of mycoplasma or chlamydia infections by PCR and culture. All 55 patients were randomly assigned to treatment with either placebo or clarithromycin 500 mg p.o. b.i.d. 6 weeks. Patients who were PCR-positive and received clarithromycin were found to have a significant improvement in FEV₁ (2.50 pretreatment, 2.69 post-treatment; $P = 0.05$), while those who were PCR negative and those who did not receive antibiotic showed no change (*Chest*. 2002; 121:1782-1788). In a related study, Turkish researchers administered azithromycin 250 mg twice weekly to a group of 11 asthmatics for 8 weeks. No change in FEV₁ was noted, but patients had a marked reduction in bronchial hyperresponsiveness as measured by histamine challenge tests. These patients were not evaluated for evidence of infection prior to initiating therapy (*J Asthma*. 2002;39:181-185).

Good News: Antibiotic Use in Children Down

Meanwhile, efforts by the CDC and others to curb the use of antibiotics in children seem to have paid off. Researchers compared antibiotic prescription rates from 1999-2000 to data from 1989-1990. The number of prescriptions per 1000 individuals age 15 and younger decreased from 838 to 503 a decade later ($P < 0.001$). Prescriptions per 1000 office visits also fell during the same period of time (*JAMA*. 2002;287:3096-3102).

Linezolid Successful in Treatment of MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA), the bane of hospitals coast-to-coast, is effectively treated with linezolid. Previously vancomycin has been the standard of care for treating MRSA. A new study compares linezolid with vancomycin in 460 patients with known or suspected MRSA infections. Patients were treated with either linezolid 600 mg twice daily ($n = 240$) or vancomycin 1 g twice daily ($n = 220$) for 7-28 days. Clinical cure rates and microbiological success rates were similar for both groups, and both regimens were well tolerated with similar rates of adverse events. It is suggestive that linezolid is a reasonable alternative to vancomycin for MRSA infections and adds the additional option of oral therapy (*Clin Infect Dis*. 2002;34:1481-1490). The study is timely, as the CDC has reported the first isolate of fully vancomycin resistant *S aureus* in a Michigan man. Several cases of intermediate vancomycin-resistant staph have been reported, but

this represents the first case of full resistance (*Morb Mortal Wkly Rep MMWR*. 2002;51:565-567).

SSRIs Relieve Dizziness in Psychiatric Patients

General internists and family practitioners will be delighted to learn that selective serotonin reuptake inhibitors (SSRIs) have been shown to effectively relieve dizziness in patients with psychiatric symptoms, a common office complaint. A group of 60 patients at University of Pennsylvania with psychogenic dizziness, dizziness due to a neurologic condition (with psychiatric symptoms), or idiopathic dizziness were treated with an SSRI for at least 20 weeks. Two thirds of patients had been treated previously with either meclizine or a benzodiazepine. Twenty-five percent of the patients did not tolerate SSRIs. Of those who finished at least 20 weeks of therapy, 84% improved substantially with no difference between patients with major psychiatric disorders and those with lesser psychiatric symptoms. Patients with peripheral vestibular conditions and migraine also improved with SSRIs (*Arch Otolaryngol Head Neck Surg*. 2002;128:554-560).

DEET-Based Mosquito Repellents Just in Time for Vacation

Just in time for summer vacation, the *New England Journal of Medicine* has published a report showing that DEET-based mosquito repellents are superior to non-DEET-based repellants. DEET is the most common compound found in commercial insect repellents. Recently, several botanical repellents have come on the market as well as 3 repellent-impregnated wristbands. These were tested against DEET containing repellents as well as one other chemical repellent containing IR3535. The worst performers were the wristbands, which offered no protection. The IR 3535-based repellents offer minimal protection while the soybean oil-based botanical repellents work for an average of 95 minutes. In comparison, the formulation containing 23.8% DEET offers complete protection for more than 300 minutes (*N Engl J Med*. 2002;347:13-18).

FDA Actions

Risedronate (Actonel), P&G Pharmaceuticals' bisphosphonate for the treatment of osteoporosis, has been approved in a 35 mg once-a-week form. The drug has been available as a 5-mg daily tablet. As with other bisphosphonates, the drug needs to be taken 30 minutes before meals, and patients must remain upright for at least 30 minutes following administration. ■