EMERGING INFECTIOUS DISEASES®

November 2009

Globally Mobile Populations

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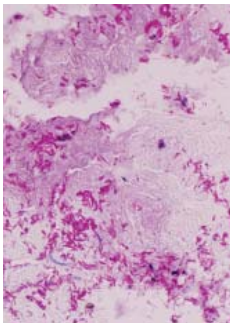

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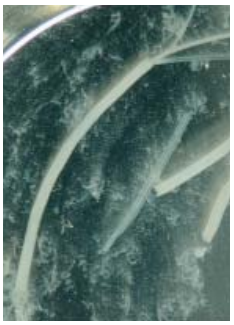

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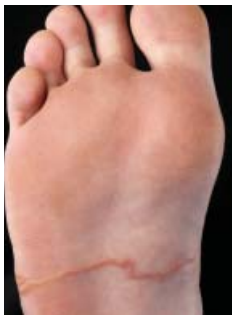

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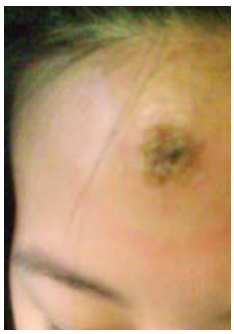

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Globally Mobile Populations and the Spread of Emerging Pathogens

Paul M. Arguin, Nina Marano, and David O. Freedman

During the past decade, the global public health community has been challenged by the emergence and rapid worldwide spread of novel influenza strains, severe acute respiratory syndrome, chikungunya virus, drug-resistant tuberculosis, and other conditions and pathogens. Modern transportation and increased tourism, business travel, and immigration contributed to dissemination of these high-impact pathogens. The effectiveness of interventions such as airport screening, travel restrictions, and other community mitigation measures remains uncertain. However, human migration has occurred for centuries and will continue, despite the threats posed by microbes.

Medicine and public health traditionally have focused on the individual pathogens. Today, however, we should look more closely at globally mobile populations that move pathogens across international borders. In addition, we should consider what travelers' behaviors, demographics, or geographic origins tell us about the microbial hitchhikers they might bring with them.

Travel and migration medicine are unique disciplines because of their dual focus on protecting the health of the individual and protecting the community in which that individual lives, works, or travels. Articles in this issue highlight globally mobile populations and stimulate thought about a recurring theme in travel and migration medicine: better identification and definition of at-risk travelers. We need to be able to identify these populations of travelers and characterize them appropriately so we can better identify modifiable risk factors and target interventions to keep travelers safe and healthy during and after their journeys.

Globally mobile population is a fairly broad, intentionally inclusive term. The fields of travel and tropical medicine usually are associated with preparing tourists for international journeys or evaluating such travelers when they return sick. Articles in this issue demonstrate a much broader concern because of the existence of many different types of globally mobile populations. This issue features articles on some of those populations: refugees, immigrants (legal and not), long-term travelers, pregnant travelers, guest workers, soldiers, cruise ship passengers, and imported animals (*1*–*6*). These extremely different popu-

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lations share a characteristic: they travel from one part of the world to another, placing themselves or others at risk for exposure to novel conditions and pathogens that can adversely affect their health.

In addition to articles about host populations are articles about populations of microbes for which epidemiologic niches have been shifted by our globally mobile populations. For example, travel and migration affect the spread of antimicrobial drug resistance, vaccine-preventable diseases, multidrug-resistant tuberculosis, novel influenza viruses, and dengue virus serotypes (*7*–*9*). The risks of travel in developing countries are known; however, imported infection also can originate in wealthy countries and on luxury cruise ships (*5*,*10*). These observations, although perhaps intuitive, help establish the foundation of the evidence base for recommendations for travel and migration medicine.

Travel and migration medicine are still fairly young fields. Much of the medical literature, including the articles in this issue, still focus on defining populations and describing diseases and conditions associated with certain groups or activities. Relatively few of these articles recommend or evaluate new interventions to keep globally mobile populations safer and healthier. Investigators and public health authorities need to start making this shift towards scientific evaluation of interventions that can lead to using this evidence to begin shifting toward recommendations for efficient, cost-effective methods to prevent illness in refugees, immigrants, and travelers. At the same time, all disease- or pathogen-specific guidelines from national and supranational bodies should explicitly address globally mobile populations. Studies that measure the impact of pretravel guidance, vaccines, and prescription of prevention or self-treatment medications will then follow.

We have many lessons to learn from the increasing number of communicable diseases associated with transportation and travel. The traveling public is our teacher; let us take this opportunity to focus on the intersection between the travel and migration medicine and public health communities to improve the control and prevention of infectious diseases in globally mobile populations.

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Health Status of Visitors and Temporary Residents, United States

Emad A. Yanni, Nina Marano, William M. Stauffer, Elizabeth D. Barnett, Maria Cano, and Martin S. Cetron

Human mobility has always been associated with the spread of infection, and mobility of nonimmigrant visitors and temporary residents to the United States is increasing, from ≈12 million in 1987 to ≈37 million in 2007. Lack of information about the health status of these populations upon arrival and their need for and use of medical services in the United States hinders development of public health policy, education, and provision of adequate clinical care. After these issues and needs are clarified, intervention programs should be developed to increase access and decrease the disparities of care experienced by these populations.

Each year, millions of nonimmigrants visit the United States. Nonimmigrants are defined by the Department of Homeland Security as foreign nationals granted temporary admission into the United States for a specific purpose (e.g., business, pleasure, academic or vocational study, or temporary employment) or to act as a representative of a foreign government or international organization (*1*). The number of nonimmigrant visitors and temporary residents to the United States increased from ≈12 million in 1987 to ≈37 million in 2007.

Human mobility has always been associated with the spread of infections such as smallpox or dengue fever. Increased speed of transportation accompanied by an exploding human population has created a situation ripe for the spread of infectious diseases. This spread of human pathogens may be manifested through an epidemic or pandemic (e.g., influenza A pandemic [H1N1] 2009 virus, HIV/AIDS, severe acute respiratory syndrome), introduction of a pathogen (e.g., West Nile virus, chikungunya virus) into a new or reestablished ecologic niche, or the spread of organisms that carry resistance or mechanisms of resistance to antimicrobial drugs (*2*). As with all mobile populations, visitors and temporary residents to the United States may represent a risk for public health through introduction of infections or vaccine-preventable diseases. Influenza A pandemic (H1N1) 2009 virus, responsible for the recent outbreak in Mexico, was subsequently transmitted across the borders to other countries, largely by returning US travelers but also through nonimmigrant visitors from Mexico (*3*). Of 178 pandemic (H1N1) 2009 patients for whom travel histories were available, 145 (82%) reported recent travel to Mexico and 4 (2%) reported travel to the United States. Among those who had not traveled to Mexico, 17 (52%) reported contact with a returning traveler from Mexico. Canada, Germany, Spain, and the United Kingdom all have reported evidence of in-country, second-generation, human-to-human virus transmission (*3*).

Although each year millions of visitors and temporary residents visit the United States, little is known about the health status of these populations. Some published reports provide a glimpse of the effects of infectious and chronic diseases carried by arriving immigrant populations, but few reports and no summarized data specifically address how visitors and temporary residents to the United States are affected by health risks such as trauma and injuries, chronic diseases, and infectious illness (*4*–*7*). Lack of information hinders development of public health policy, education, and provision of adequate clinical care for visitors and temporary residents. Therefore, to raise awareness of this traveling population, we have summarized the sparse available literature and call for future education, policies, and inter-

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ventions geared toward promoting health and well-being for the visitors and temporary residents and public health protection to host communities.

Description of Visitors and Temporary Residents to the United States

During 2007, a total of 171 million nonimmigrants were admitted to the United States: 134 million (78%) were Canadian and Mexican travelers who acquired border-crossing cards for the purpose of tourism or business, and 37 million (22%) were travelers with I-94 forms (applications required for nonimmigrant admission to the United States; Mexican nationals with border-crossing cards and tourists and business travelers from Canada are generally exempt from the I-94 requirement) (*1*). Most persons admitted with I-94 forms were temporary visitors such as tourists and business travelers (33.3 million; 89%), short-term residents (3.6 million; 10%), and expected long-term residents (205,000; 1%). Those admitted as temporary residents included short-term residents (e.g., temporary workers and families, students, exchange visitors [students participating in an exchange program], diplomats) and long-term residents (e.g., alien fiancés and spouses of US citizens or permanent residents and their children). Nonimmigrant admission refers to the number of events (entries into the United States) rather than persons. In 2007, the 10 countries with the most I-94 form admissions to the United States were India (11%), Mexico (11%), Japan (7.5%), United Kingdom (6.3%), South Korea (6%), Canada (6%), Germany (4%), People's Republic of China (4%), France (3%), and Brazil (2%). From 2006 through 2007, the largest increases in resident nonimmigrant admissions came from citizens of Mexico (36% increase), India (30% increase), and China (27% increase), largely accounted for by increased numbers of seasonal workers, academic students, workers in specialty occupations, and intracompany transferees (*1*). From 2005 through 2007, the 10 most common destination states were California (14%), New York (13%), Texas (8.2%), Florida (7.7%), New Jersey (4.4%), Massachusetts (4%), Illinois (3.4%), Virginia (3.2%), Michigan (2.8%), and Pennsylvania (2.7%). The first 5 states represented the declared destinations of nearly 50% of the foreign nationals admitted in 2007 (*1*).

A study by the Office of Immigration Statistics estimated that during 2004, on any typical day, 3.8 million visitors and temporary residents were in the United States: 2.3 million (61%) tourist and business travelers, 704,000 (18%) temporary workers, and 640,000 (17%) students and exchange visitors (*8*). The mean lengths of visit were as follows: tourists and business travelers, 22 days; diplomats, 13 weeks; temporary workers, 23 weeks; students and exchange visitors, 31 weeks; and long-term residents, 43 weeks (*8*).

Health Regulations for Visitors and Temporary Residents to the United States

Health requirements that pertain to applicants for an immigrant–permanent resident visa do not apply to visitors and temporary residents. The current US immigration laws require applicants for an immigrant visa to have mandatory medical screening for some infectious diseases and to have up-to-date, age-dependent vaccination coverage before an immigration visa will be issued. Visitors and temporary residents do not receive medical screening for infections such as tuberculosis (TB) and are not required to fulfill US vaccination requirements. No surveillance system is in place to identify health problems in this population. Therefore, medical conditions are known only if a person has a reportable disease, for which reporting to health departments is mandatory. Occasionally, case reports or case series published in academic journals shed some light on health issues encountered. We therefore examined these limited reports on vaccination coverage, disease burden, and healthcare-seeking behavior of nonimmigrant travelers.

Specific Populations of Nonimmigrants to the United States

Temporary Residents: International Students and Exchange Visitors

Persons who travel to the United States to study may represent a population at higher risk than others for transmission and spread of infectious diseases. Risk is increased because college campuses provide favorable environments or situations for spread of infectious diseases, e.g., close contact (e.g., in classrooms, in dormitories, and at social gatherings), student behavior, and variable immunity among persons from a wide geographic area (*9*).

In 2008, an estimated 1,052,694 active nonimmigrant students and exchange visitors and their families were in the United States; 68% were enrolled in bachelor, masters, or doctoral degree programs (*10*). The 5 countries from which most international students originated were South Korea, India, China, Japan, and Taiwan. In 2008, the states that hosted more than half (51%) of all enrolled international students were California, New York, Texas, Massachusetts, Illinois, and Florida (Map 1 in the online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1715-Techapp.pdf). Despite this large number of international students, no published data are available regarding their vaccination coverage.

Prevalence of TB varies worldwide and may affect nonimmigrant travelers. In a study conducted during 1997–1998 among incoming international students from 70 countries enrolled in a community college in Iowa, 59 (35%) of 171 had a positive tuberculin skin test result (≥10 mm induration). Of those 59, isoniazid therapy was begun by

34, of which 27 successfully completed the prescribed regimen (*11*). The Iowa study suggests that treatment of latent TB infection in visiting student populations is suboptimal and may represent an area in which improved intervention could prevent illness and spread of infection.

Temporary Residents: Agricultural Workers

Another group of temporary residents comprises agricultural workers and their families. The Department of Homeland Security defines farm workers as agricultural workers, but other agencies consider them farm workers, crop workers, or agricultural workers. For instance, the federal statutes governing migrant health funds define a migrant farm worker as a person who mainly works in agriculture on a seasonal basis and may migrate from farm to farm within a state, among states, or among countries (*12*).

According to the 2005 National Agriculture Workers Survey results, a large percentage (42%) of agriculture workers in 2001–2002 were migrants. Among the migrants, 26% traveled only within the United States and 35% migrated repeatedly to and from a foreign country (*13*). The Survey also reported that 78% of agricultural workers were foreign born, 50% were younger than 31 years of age, 80% were male, 58% were married, and 57% were living apart from their families (*13*). Of the estimated 3 million seasonal agricultural workers in the United States in 2006, 1 million were hired agricultural workers, ≈50% of whom lacked legal authorization to work in the United States (*14*).

In terms of health status, seasonal agricultural workers frequently live in crowded conditions with poor sanitation and may have suboptimal nutrition; each of these factors is associated with spread of infectious disease. The characteristics of this group may predispose them to infection with, and spread of, TB. In 1996, a study among Hispanic migrant agricultural workers in Indiana found that 28.3% of adult and 7.5% of adolescent (11–18 years of age) agricultural workers had a positive tuberculin skin test result, although no active TB cases were identified. The study also found a high rate of chronic respiratory diseases, which may predispose this population to further consequences of superimposed acute or chronic respiratory infections (*15*). This large mobile population has all factors known to be associated with HIV/AIDS and sexually transmitted infections: members are generally young, mostly male, live in poverty, and have limited access to educational opportunities (*12*,*16*).

Agricultural workers may also be disproportionately prone to injuries and exposed to environmental health hazards. One study reported that 6% of male and 4% of female agricultural workers had at least 1 workplace injury during the 12-month period before the interview (*17*). Other studies have shown that direct contact with pesticides is frequently associated with multiple workplace health conditions, such as irritated eyes, headache, blurred vision, dizziness, numbness, tingling, diarrhea, vomiting, and skin irritation (*18*,*19*). Recent research on the mental health of agricultural workers has found that nearly 40% of workers experience depression and 30% experience anxiety (*20*). A cohort study among agricultural workers in Colorado found pesticide poisoning to be significantly associated with depression (*21*).

The California Agricultural Workers Health Survey, conducted in 2000, found that rates of chronic health conditions for agricultural workers were high; e.g., 81% of male and 76% of female agricultural workers were overweight or obese, predisposing them to diabetes and heart disease (*22*). Lack of available health insurance clearly creates barriers to care and substantially limits access to healthcare services, exacerbating disparities (*6*,*7*). Although 23% of seasonal agricultural workers reported having some type of health insurance, only 8% of seasonal workers and 15% of year-round workers reported that their employer offered them insurance for non–work-related illness or injury (*13*). Even workers who have access to health insurance through employee premium share programs frequently do not enroll because they cannot afford the premiums (*13*). Although compelling information indicates the need for action to serve this vulnerable population, more detailed and systematic data collection would assist in crafting better policies, interventions, and educational tools and materials.

Visitors: Tourists and Business Travelers

Travel of susceptible or infected persons from disease-endemic to disease-nonendemic areas presents an opportunity for transmission of vaccine-preventable diseases in susceptible populations. This risk is especially great when vaccination rates in disease-nonendemic areas are declining or low. Although national vaccination levels are high in the United States, unvaccinated children tend to be clustered geographically or socially, increasing the risk for transmission of vaccine-preventable diseases (*23*,*24*). Every year, ≈17,000 children in the United States receive no vaccine, primarily for religious, personal, or medical reasons (*24*). Most of these children reside in states that allow exemptions to laws mandating vaccinations for children as they enter school (*24*). During 2000–2001, all states allowed vaccination exemptions for medical reasons, 48 for religious reasons, and 12 for philosophical reasons. Of the states that allow exemptions, 6 (California, Texas, New York, Florida, Illinois, and New Jersey) are also the states of residence for 68% of the children of US immigrants (*25*). These states also receive the largest number of nonimmigrant temporary residents (*1*). The proximity of susceptible populations to large numbers of mobile visitors and temporary residents may represent opportunities for potential sustained transmission of vaccine-preventable diseases.

A recent experience in Europe highlights the risk of allowing vaccination rates to decline. In June 2008, the United Kingdom's Health Protection Agency declared that measles was again endemic there as a result of an 80%–85% decline in measles vaccination coverage among children <2 years of age (*26*). This decline in coverage resulted from an increase in the number of parents who refused to have their children vaccinated. During the same period, Austria, Italy, and Switzerland also reported measles outbreaks (*27*,*28*). As noted earlier, in 2007 the United Kingdom was among the 4 most common countries of citizenship for short-term temporary residents in the United States (*1*). Although measles was declared eliminated in the United States in 2000, during the first 7 months of 2008, the US Centers for Disease Control and Prevention reported measles outbreaks in 15 states (*29*). Of the 131 confirmed cases, 89% were imported from or associated with importation from other countries, particularly from the previously mentioned countries in western Europe; 91% were in persons who were unvaccinated or of unknown vaccination status. Among the 131 cases, 17 were acquired outside the United States, 9 were in US residents who had traveled, and 8 were in visitors and temporary residents. Among the 112 (91%) confirmed measles cases in unvaccinated persons, 63 (66%) of these persons had not been vaccinated because of philosophical or religious beliefs (*29*). The 2008 measles outbreaks demonstrated the risk for transmission of communicable diseases by travelers returning to the United States and by visitors and temporary residents visiting communities where clusters of people have suboptimal vaccine coverage (Map 2 in the online Technical Appendix).

Poliomyelitis is another vaccine-preventable disease that has been reintroduced through mobile populations. During 2003–2006, polio was imported by travelers (e.g., refugees, pilgrims, business travelers) to 24 polio-free countries (*30*). In 2005, the Minnesota State Health Department diagnosed vaccine-derived poliovirus infection in 4 children; the infection had been circulating in 4 children in a predominantly unvaccinated religious community (*31*). No source for the infection could be identified, but the original source of this virus was probably a person who had received oral polio vaccine in another country. Neither the index case-patient nor her family members had any history of international travel. This outbreak raised concerns regarding transmission of the virus to other US communities with low vaccination levels (Map 3 in the online Technical Appendix).

TB is a major health problem for US residents and visitors who were born in or have lived in Asia, Africa, Latin America, or eastern Europe, where TB remains highly endemic (*32*). In 2007, the overall incidence of TB in the United States was 4.2 cases per 100,000 population; rates were 2.1 per 100,000 population for US-born persons and 20.6 per 100,000 for foreign-born persons. More than half (51.8%) of foreign-born persons with TB were from 4 countries: Mexico (n = 1,846), the Philippines (n = 952), India (n = 619), and Vietnam (n = 568). Of all reported TB cases in the United States during 2007 (n = 13,292), 52% were reported by the 5 most common destination states for immigrants and visitors and temporary residents (California, Florida, Illinois, New York, and Texas) (*1*,*10*,*33*). A study published in 2004 found that 42% (n = 114) of TB culture–positive cases diagnosed by the Tarrant County Health Department in Texas from 1998 through 2000 were in foreign-born persons. Of these, 67 (59%) were permanent residents, 28 (25%) were undocumented, and 19 (17%) were visitors or temporary residents (*34*).

Many persons may visit the United States without seeking pretravel health consultation. Certain areas in the United States have endemic diseases that visitors and temporary residents are not familiar with such as Lyme disease, Rocky Mountain spotted fever, and West Nile virus encephalitis.

Current Efforts to Improve the Health Status of Temporary Residents

To improve the health of nonimmigrant temporary residents, government agencies and nongovernment advisory groups are making efforts to ensure that certain categories of nonimmigrant visa applicants are aware of and have access to healthcare services while in the United States. The US Department of State requires exchange visitors (J-1 visa category) and their dependents (J-2 visa category) to have their own medical insurance coverage and enlists program sponsors to ensure compliance with requirements (*35*). However, no similar federal guidance exists for other categories of nonimmigrant visa holders.

In March 2008, the American College Health Association (ACHA) updated its guidelines for student health insurance program standards (*36*). According to these guidelines, as a condition of enrollment students must provide evidence of adequate health insurance coverage for themselves and their dependents. Because of concerns about the spread of vaccine-preventable diseases on college campuses, ACHA also updated its recommendations for prematriculation immunizations to be consistent with the recommendations of the Advisory Committee on Immunization Practices (*37*). In addition, to address the shifting epidemiology of TB to foreign-born persons, ACHA updated its TB control guidelines in July 2008. The new guidelines recommend that US colleges and universities screen all incoming students for active or latent TB (*38*). Resources have been developed to help US colleges and universities institute screening and treatment programs (*39*).

More broadly, many health systems, with substantial support from federal agencies, have begun to meet the healthcare needs of farm workers and their families, such

as the federally qualified nonprofit community and migrant health centers that provide primary and preventive health services throughout the United States. The Health Resources and Services Administration, through the Bureau of Primary Care, has developed the Health Disparities Collaborative Program to eliminate ethnic health disparities (*12*) through their health centers and mobile clinics that serve remote farms. In addition, a grassroots movement among local clinics and organizations (the Migrant Clinician Network) has developed tools and materials to support clinics and clinicians who work with farm workers (www.migrantclinician.org).

Many states have begun to develop guidance for providing medical and preventive health services to mobile populations (e.g., immigrants, and refugees), especially in states with a high percentage of these populations, such as Minnesota, Massachusetts, Michigan, New York, and California. These states have identified culturally and linguistically appropriate ways to address the health concerns of foreign-born persons. An exemplary program for linguistically and culturally appropriate healthcare education material in multiple media is the Emergency, Community and Health Outreach network (http://newroutes.org/echo).

In addition to government agencies, several academic institutions and many integrated health systems and even community clinics have begun to train future providers in culturally sensitive and geographically informed healthcare. The number of Academic Global Health Centers in the United States has surged; some programs offer training in the special health issues of mobile populations (*40*).

Although many government agencies, nonprofit organizations, academic institutions, integrated health systems, clinics, and individuals are developing innovative programming and materials, all these efforts are in their infancy and generally not well coordinated. To substantially reduce the disparities of care experienced by mobile populations, including visitors and temporary residents, we need improved data collection, surveillance and scientific evaluation, changes in systems to reduce barriers to care, and increased education and advocacy on behalf of these frequently disenfranchised populations.

A relatively simple, concrete step that could be taken is the development of health awareness programs that try to reach visitors and temporary residents before their arrival in the United States. Such programs could acquaint visitors and temporary residents with US health service requirements and regulations and reduce the burden on the public healthcare system. This goal could be achieved by developing innovative communication tools and messages that address the following: access to the public healthcare system, the Advisory Committee on Immunization Practices vaccination recommendations, and the health insurance coverage policies available in the United States. These messages could be disseminated by many organizations, including the US Department of State, the Centers for Disease Control and Prevention, US university clinics, American cultural centers and education offices at US embassies overseas, health and travel insurance companies that provide emergency health insurance coverage to visitors to the US, and the offices of international banks solicited by the US embassies to receive visa processing fees and distribute visa application forms. Ultimately, to better serve visitors and temporary resident populations, particularly vulnerable populations such as farm workers, more equitable care models and evidence-based clinical best practices must be developed and disseminated.

Conclusions

Nonimmigrant visitors and temporary residents represent a considerable and increasing percentage of travelers to the United States (*1*). Information is limited with regard to the health status of visitors and temporary residents upon arrival and their need for and use of medical services in the United States. More information is needed to determine the public health issues as well as the health challenges and needs of visitors and temporary residents in the United States. After these issues and needs have been clarified, intervention programs should be developed to increase access and decrease the disparities of care experienced by these populations.

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Risk of Importing Zoonotic Diseases through Wildlife Trade, United States

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The United States is the world's largest wildlife importer, and imported wild animals represent a potential source of zoonotic pathogens. Using data on mammals imported during 2000–2005, we assessed their potential to host 27 selected risk zoonoses and created a risk assessment that could inform policy making for wildlife importation and zoonotic disease surveillance. A total of 246,772 mammals in 190 genera (68 families) were imported. The most widespread agents of risk zoonoses were rabies virus (in 78 genera of mammals), *Bacillus anthracis* (57), *Mycobacterium tuberculosis* complex (48), *Echinococcus* spp. (41), and *Leptospira* spp. (35). Genera capable of harboring the greatest number of risk zoonoses were *Canis* and *Felis* (14 each), *Rattus* (13), *Equus* (11), and *Macaca* and *Lepus* (10 each). These findings demonstrate the myriad opportunities for zoonotic pathogens to be imported and suggest that, to ensure public safety, immediate proactive changes are needed at multiple levels.

Most emerging infectious diseases are caused by zoonotic pathogens (*1*,*2*). The number and proportion of these diseases that originate in wild animals in particular has increased substantially in the past few decades, even after accounting for increased reports of new emerging infectious diseases (*1*). This trend and recent pandemics of wildlife-origin infectious diseases (e.g., HIV, severe acute respiratory syndrome) suggest that targeted surveillance efforts should focus on activities that bring humans and wildlife in close contact (*1*,*3*).

The United States is among the world's largest importers of live wild animals (*4*) and imported >1 billion individual animals during 2000–2004 (*5*). Little disease surveillance is conducted for imported animals; quarantine is required for only wild birds, primates, and some ungulates arriving in the United States, and mandatory testing exists for only a few diseases (psittacosis, foot and mouth disease, Newcastle disease, avian influenza). Other animals are typically only screened for physical signs of disease, and pathogen testing is delegated to either the US Department of Agriculture (for livestock) or the importer (*6*). The process of preimport housing and importation often involves keeping animals at high density and in unnatural groupings of species, providing opportunities for cross-species transmission and amplification of known and unknown pathogens. Thus, imported wildlife remain a major public health threat, as exemplified by the importation of Ebola virus in primates from the Philippines (*7*), monkeypox from imported African rodents (*8*), and possibly HIV from chimpanzees in central Africa (*9*). Wildlife importation also poses a great threat to domestic wildlife and the US agriculture industry (*5*).

To analyze the volume and diversity of live mammals that have been imported into the United States in recent years, we used data from the US Fish and Wildlife Service Law Enforcement Management Information System. We focused on mammals because of the frequency and severity of previously reported mammal-borne zoonoses and because of the frequent close association between humans and many mammalian species (e.g., as pets). We then assessed the zoonotic diseases that imported mammals are known to host. Our results may be used to inform policy decisions about wildlife importation and zoonotic disease surveillance and may alert clinicians to the broad range of possible zoonoses that may be encountered in patients who have been exposed to imported animals.

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Methods

We used Freedom of Information Act requests to obtain records from the database of the US Fish and Wildlife Service Law Enforcement Management Information System. We obtained records for all wildlife shipments into the United States during 2000–2005 through 14 of the 18 designated animal importation ports (Anchorage, Alaska; Atlanta, Georgia; Baltimore, Maryland; Boston, Massachusetts; Chicago, Illinois; Dallas, Texas; Honolulu, Hawaii; Los Angeles, California; Miami, Florida; New Orleans, Louisiana; New York, New York; Portland, Oregon; San Francisco, California; and Seattle, Washington). Data were not available for Houston, Texas; Louisville, Kentucky; Memphis, Tennessee; and Newark, New Jersey. For each importation, we acquired information on the taxonomy, quantity, source (e.g., wild-caught, farmed), country of origin, intermediate port of call, port of entry, and declared purpose of all live specimens. Descriptive analyses were performed to determine the volume of trade from various regions of the world and the types of mammals imported. Individual importation events were then grouped into genera to determine the diversity of taxa imported. The phylogenetic relationships and geographic ranges of host mammals were determined by using the Animal Diversity Web at the University of Michigan Museum of Zoology (http://animaldiversity.ummz.umich.edu/site/index.html).

We searched the literature to identify the zoonotic pathogens known to occur in animals of each taxon in the database. Only data on live animal importations (as opposed to animal products) and importations for which the genus was known were retained for analysis. Statistical analyses were performed by using Intercooled Stata 9 (StataCorp, College Station, TX, USA). In our final risk assessment, we did not account for the origin of each specific importation because of limitations in the database, likely caused by a complicated system of exportation and reimportation.

We created a list of relevant zoonotic diseases at risk for importation (hereafter referred to as risk zoonoses) by searching the Centers for Disease Control and Prevention website (www.cdc.gov) and the World Health Organization website (www.who.int), reviewing the list of Select Agents (agents with bioterrorism potential) of the US Department of Health and Human Services (*10*), and consulting experts in the field. To be on the list, diseases had to meet the following 5 criteria: 1) the pathogen must be zoonotic (there must be a recorded instance of infection of a human from an animal source); 2) the pathogen must be capable of causing significant illness or death (e.g., fungal skin infections would not be on the list because although they are extremely common zoonoses, their effects are rarely debilitating); 3) the pathogen must be present in animals in the wild (i.e., not only in experimental models); 4) the pathogen must not currently be widespread in the United States, or it must have the potential for new epidemiology with regard to transmission (e.g., *Yersinia pestis* is presently found in wild rodents in the western United States, but it is not expected to be found in animals sold as pets); and 5) if the pathogen uses an intermediate vector, competent vectors must exist in the United States. The resulting list comprised 30 risk zoonoses (20 viral diseases, 9 bacterial diseases, and 1 helminthic disease); no fungal, protozoal, or prion diseases were on the list, and thus they were not analyzed.

Determination of the host range of the risk zoonoses was accomplished through systematic genus-driven and pathogen-driven searches of PubMed databases (www.pubmed.gov), the Google search engine (www.google.com), and references within published works. Confirmed presence was defined as either isolation of the pathogen from an animal or serologic evidence of past infection. For all animals identified in the literature as carrying a risk zoonosis, genus and family were recorded. The host ranges of all of the risk zoonoses were then cross-referenced against the imported genera to generate tables showing diseases found in each imported genus (affected genera). If the disease was found in a different genus within the same family, this was also noted (potentially affected genera). The justification for this expanded risk assessment is the host nonspecificity of many infectious diseases; lack of evidence for the presence of a given disease in a given host should not be construed as evidence against its presence.

Results

During 2000–2005, a total of 4,067 shipment fractions of mammals were imported (a shipment fraction is the sum of all animals of a single species in a given shipment; a single shipment may contain several shipment fractions), totaling 246,772 individual mammals and representing 190 genera and 68 families. The average number of animals per shipment fraction was 61 (range 1–8,000). The most common declared purpose for importation was commercial use (not classified according to pet trade, food, traditional medicine, etc.), accounting for 66% (163,760 individuals) of the total. The second most common declared purpose was biomedical research, accounting for 28% (69,986 individuals) of the total. Only a small number of individuals were imported for breeding, educational, zoo, personal, and other uses. Numbers of the most commonly imported animals were 126,014 (>50% of all imported individuals) long-tailed macaques (*Macaca fascicularis*), 30,058 small desert hamsters (*Phodopus sungorus*), 19,724 rhesus macaques (*Macaca mulatta*), 19,537 raccoons (*Procyon lotor*), and 7,112 chinchillas (*Chinchilla lanigera*). Together, these 5 species accounted for 82% of all imported individuals. By number of shipment fractions, the most common animals were 1,343 *M. fascicularis* macaques, 332 *Cal-*

lithrix jacchus marmosets, 229 *M. mulatta* macaques, 165 *C. lanigera* chinchillas, and 107 *Potos flavus* kinkajous.

The most common countries of origin for animal shipment fractions were People's Republic of China (717 shipment fractions); Guyana (635), United Kingdom (359), Vietnam (314), and Indonesia (305). These values must be interpreted cautiously, however, because many animals are imported and then reexported; thus, their true origin may become obscured. For example, a "wild-caught" chinchilla with a "country of origin" of Czech Republic must have originated elsewhere because chinchillas are native to Chile. A comparison between the natural geographic range of all wild-caught animals and their stated countries of origin showed that >25% of the pairings were impossible (i.e., the animals could not have come from their stated country of origin). This limitation is inherent in the way US Fish and Wildlife Service Law Enforcement Management Information System data are collected, and we were unable to correct these data.

The source of the animals was largely uninterpretable because 49% of all individuals were declared as being sourced from "animal derivatives and parts," despite the fact that we had selected only live animals for our analysis, and despite the fact that "animal derivatives and parts" is not one of the permitted responses to this question. Another 29% were declared as "captive-bred" and 15% as "wild-caught."

For the final list of risk zoonoses, 3 of the original 30 agents (Hendra virus, Menangle virus, and *Rickettsia prowazekii*) were removed because few, if any, genera were found to harbor these infections; the final tables therefore include 27 diseases (Tables 1–3). The risk zoonoses capable of infecting the greatest number of genera were: rabies viruses, in 78 genera; *Bacillus anthracis*, the causative agent of anthrax, in 57 genera; *Mycobacterium tuberculosis* complex, in 48 genera; *Echinococcus* spp., the agents of hydatid cyst disease, in 41 genera; *Leptospira* spp., in 35 genera; *Brucella* spp., the agents of undulant fever, in 32 genera; *Francisella tularensis*, the agent of tularemia, in 31 genera; Crimean-Congo hemorrhagic fever virus, in 27 genera; *Y. pestis*, the agent of plague, in 24 genera; and *Coxiella burnetii*, the agent of Q fever, in 20 genera (Table 2; online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1721-Techapp.pdf).

If each genus within affected families is counted as potentially capable of harboring a risk zoonosis (according to the principle that many diseases are not entirely host specific), the number of genera potentially capable of harboring rabies viruses rises to 155 (82% of all imported taxa); potential carriers of *Leptospira* spp. increase to 131; *M. tuberculosis* complex to 124; *F. tularensis* to 115; *B. anthracis* to 113; *C. burnetii* to 108; and *Y. pestis* to 101.

The genera capable of harboring the greatest number of risk zoonoses were *Canis* (dogs) and *Felis* (cats), 14

Table 1. Risk zoonoses and their associated clinical syndromes in humans*

Pathogen	Primary clinical syndrome in humans
Viruses	
Lymphocytic choriomeningitis virus	Aseptic meningitis
Cercopithecine herpesvirus-1 (herpes B)	Encephalitis
Nipah virus	Encephalitis
Rabies viruses†	Encephalitis
Venezuelan equine encephalitis virus	Encephalitis
Tick-borne encephalitis virus complex†	Encephalitis or hemorrhagic fever
Crimean-Congo hemorrhagic fever virus	Hemorrhagic fever
Ebola viruses†	Hemorrhagic fever
Lassa fever virus	Hemorrhagic fever
Marburg virus	Hemorrhagic fever
Rift Valley fever virus	Hemorrhagic fever
South American hemorrhagic fever arenaviruses†	Hemorrhagic fever
Hantaviruses associated with HFRS†	Hemorrhagic fever with nephropathy
Hantaviruses associated with HCPS†	Severe respiratory syndrome
Highly pathogenic avian influenza (H5N1) virus	Severe respiratory syndrome
SARS virus (or SARS-like CoV)	Severe respiratory syndrome
Yellow fever virus	Systemic illness or hemorrhagic fever
Monkeypox virus	Systemic illness or rash
Bacteria	
Brucella spp.	Systemic illness
Coxiella burnetii	Systemic illness
Leptospira spp.	Systemic illness
Bacillus anthracis	Varies by site of infection
Burkholderia mallei	Varies by site of infection
Francisella tularensis	Varies by site of infection
Mycobacterium tuberculosis complex†	Varies by site of infection
Yersinia pestis	Varies by site of infection
Helminths, *Echinococcus* spp.	Hydatid cyst disease

*Risk zoonoses, relevant zoonotic diseases at risk for importation into the United States; HFRS, hemorrhagic fever with renal syndrome; HCPS, hantavirus cardiopulmonary syndrome; SARS, severe acute respiratory syndrome; CoV, coronavirus.
†Rabies viruses includes the zoonotic lyssaviruses Australian bat lyssavirus, Duvenhage, European bat lyssavirus 1 and 2, Mokolo, and rabies (*11*); tick-borne encephalitis complex includes Kyasanur Forest disease, Omsk hemorrhagic fever, and tickborne encephalitis (*11*); Ebolaviruses include Bundibugyo, Côte d'Ivoire, Reston, Sudan, and Zaire (*11*); epidemiologically relevant South American hemorrhagic fever arenaviruses include Guanarito, Junin, Machupo, and Sabia (*11*); hantaviruses associated with HFRS include Dobrava, Hantaan, Puumala, Saaremaa, and Seoul (*11*); hantaviruses associated with HCPS include Andes, Bayou, Black Creek Canal, Laguna Negra, New York, and Sin Nombre (*11*); *Mycobacterium tuberculosis* complex species are *M. africanum, M. bovis, M. bovis BCG, M. caprae, M. microti, M. pinnipedii,* and *M. tuberculosis hominis* (*12*).

Table 2. Risk zoonoses capable of infecting the greatest number of imported mammal genera

Pathogen	No. (%) affected genera*	No. (%) potentially affected genera†
Rabies viruses‡	78 (41)	155 (82)
Bacillus anthracis	57 (30)	113 (59)
Mycobacterium tuberculosis complex‡	48 (25)	124 (65)
Echinococcus spp.	41 (22)	89 (47)
Leptospira spp.	35 (18)	131 (69)
Brucella spp.	32 (17)	95 (50)
Francisella tularensis	31 (16)	115 (61)
Crimean-Congo hemorrhagic fever virus	27 (14)	91 (48)
Yersinia pestis	24 (13)	101 (53)
Coxiella burnetii	20 (11)	108 (57)

*Risk zoonosis (relevant zoonotic disease at risk for importation into the United States) identified in genus; n = 190.
†Risk zoonosis identified in different genus within same family; n = 190.
‡Risk zoonoses, relevant zoonotic diseases at risk for importation into the United States. Refer to Table 1 footnote for explanation of pathogen complexes.

risk zoonoses each; *Rattus* (rats), 13; *Equus* (horses), 11; *Macaca* (macaques), 10; *Lepus* (rabbits and hares), 10; and *Ovis* (sheep) and *Vulpes* (foxes), 9 each (Table 3). Of the individuals in these high-risk genera, 49% were intended for commercial purposes and 44% were intended for biomedical research.

The families found to harbor the most risk zoonoses (excluding Hominidae because, by definition, they are capable of harboring all zoonotic diseases) were Muridae (Old World mice and rats, gerbils, whistling rats, and relatives), 21 risk zoonoses; Cricetidae (New World rats and mice, voles, hamsters, and relatives), 20; Canidae (coyotes, dogs, foxes, jackals, and wolves), 16; and Bovidae (antelopes, cattle, gazelles, goats, sheep, and relatives) and Felidae (cats), 15 each.

Discussion

Our data demonstrate that myriad opportunities exist for key zoonotic pathogens to be imported into the United States or, if already present, to be introduced in a new context (e.g., in an animal sold as a pet). Imported animals of a large number of taxa were found to be capable of carrying risk zoonoses; these diseases include such serious public health threats as rabies, the filovirus hemorrhagic fevers, tuberculosis, and highly pathogenic avian influenza.

This study likely underestimates the broad nature of risk associated with the importation of wild animals. We examined only families in the class Mammalia that have been shown to harbor risk zoonoses; however, many pathogens routinely cross boundaries at least as high as the class level (e.g., human psittacosis from birds), if not higher. Furthermore, we included only live animals in this analysis; recent outbreaks associated with animal products (e.g., cutaneous anthrax from an imported goat hide used for making drums) attest to the risks associated even with dead animals (*13*). Finally, the study can neither estimate the risk for unknown pathogens, which may be imported but not yet identified, nor assess the volume and zoonotic risk created by illegal wildlife trade. Animals may be smuggled specifically because they have been banned from trade as a result of perceived or recognized health threats. Some animals on our list of risk zoonoses have already been banned from importation (e.g., masked palm civets, birds from countries affected by highly pathogenic avian influenza [H5N1]) (*14*). However, pathogens have been identified in illegally imported wildlife; e.g., a pair of crested hawk-eagles (*Spizaetus nipalensis*) smuggled from Thailand and recently confiscated in Belgium were infected with highly pathogenic avian influenza (H5N1) (*15*).

We did not quantitatively assess the risk for transmission of each pathogen at each importation event. Rather, we attempted to demonstrate the breadth of risk associated with importations of wild animals in general. Quantitative prevalence of the various pathogens in each wildlife host is highly variable, and determining it is beyond the scope of our analysis. Some genera represent the primary reservoirs of certain pathogens (e.g., *Peromyscus* for certain hantaviruses), whereas proof of the permissiveness of other genera to certain pathogens is limited to isolated case reports (e.g., Ebola Zaire virus in the duiker *Cephalophus*). Perhaps the greatest unknown associated with quantifying risks for each of the zoonoses is a pathogen's infectivity in various hosts. Some pathogens may increase to a high enough load in their hosts to be infectious; others may cause nothing more than a measurable serologic response in what is otherwise a dead-end host (though explicitly known dead-end hosts have been excluded from these analyses).

Our analysis highlights several ways that the US Fish and Wildlife Service could improve data collection. To enhance public health officials' ability to trace back the sources of imported zoonotic diseases, record keeping of the point of origin of shipments could be expanded to include not just their most recent and previous point of origin (as is currently done with the "Country of Origin" and "Country of Importation/Exportation/Re-importation") but

Table 3. Mammal genera capable of harboring the greatest number of risk zoonoses*

Genus (common name)	No. (%) risk zoonoses
Canis (dogs)	14 (52)
Felis (cats)	14 (52)
Rattus (rats)	13 (48)
Equus (horses)	11 (41)
Macaca (macaques)	10 (37)
Lepus (rabbits and hares)	10 (37)
Ovis (sheep)	9 (33)
Vulpes (foxes)	9 (33)

*Risk zoonoses, relevant zoonotic diseases at risk for importation into the United States; n = 27.

also their actual origin. Accurate recording of the source of the animals (e.g., wild-caught, captive-bred) is also needed. Our results showed that half of all individuals had a declared source that was not one of the allowed choices (e.g., wild-caught, captive-bred). The source of an animal affects not only the likely level of risk (i.e., one would expect captive-bred individuals to carry fewer zoonotic diseases than wild-caught individuals) but also mitigation strategies when zoonotic diseases are identified (e.g., euthanizing a colony vs. improving quarantine after capture).

The potential for importation of zoonoses that would pose a major public health threat suggests that increased surveillance should be applied to imported wildlife in the United States. One opportunity to reduce this threat is restriction of importation of key high-risk species, as was done when the Centers for Disease Control and Prevention used emergency powers to restrict importation of Gambian pouched rats during the monkeypox outbreak (*14*). Given the great diversity of animals identified by our analysis as potentially hazardous, broad importation bans would likely be necessary if the goal were to substantially decrease the overall risk. Political or social support may be limited for such broad bans, both in the United States (as one of the world's largest purchasers of wildlife) and abroad (where wildlife trade can have profound economic benefits).

Furthermore, illegalizing trade may only increase underground (illicit) trade, thereby eliminating the possibility of screening shipments for potential hazards. A more effective and acceptable strategy would be enhancing surveillance for the specific pathogens noted for the key risk genera (those harboring the greatest number of risk zoonoses, i.e., *Canis, Felis*, *Rattus*, *Equus*, *Macaca*, *Lepus*, *Ovis,* and *Vulpes*). Notably, the numbers of shipments of mammals is low relative to other wildlife groups (e.g., fish and reptiles). Lawmakers' interests in protecting our borders from external bioterrorism threats intersect with the need to protect ourselves from zoonotic diseases; many Category A bioterrorism threats (e.g., anthrax, plague, tularemia, and the viral hemorrhagic fevers) (*10*) are represented in the risk zoonoses outlined above. Finally, to facilitate the standardization of surveillance and detection of infection events, the Council of State and Territorial Epidemiologists should include all of the risk zoonoses among their states' notifiable diseases (most of which are already included).

Perhaps one of the simplest practical interventions for minimizing zoonotic disease risk is reduction of opportunities for transmission from wildlife to humans. Although a large proportion of imported animals are destined for biomedical research (in which potential occupational risks are largely understood and quarantine procedures likely mitigate risk), a greater proportion (even among the high-risk genera) are destined for commercial use and therefore could expose a wider group of persons to zoonotic diseases. Education of professionals likely to come in close contact with imported animals (e.g., veterinarians, importers, pet store employees), as well as the general public, should emphasize the risks for contracting zoonotic diseases from wildlife and pets (*16*) and the need for proper hygiene, safety procedures, and personal protective equipment (*17*).

The recommendations above mirror others that exist in policy documents by the Defenders of Wildlife (*5*), in the 2003 joint position statement by the National Association of Public Health Veterinarians and the Council of State and Territorial Epidemiologists (*18*), and in a recent Policy Forum article (*19*). These reports describe clear steps for mitigating the risks presented by imported wildlife, yet their recommendations have so far gone largely unheeded. To ensure public safety, immediate proactive changes are needed at multiple levels. Such measures would be most effective if organized in consultation with groups involved in the wildlife trade.

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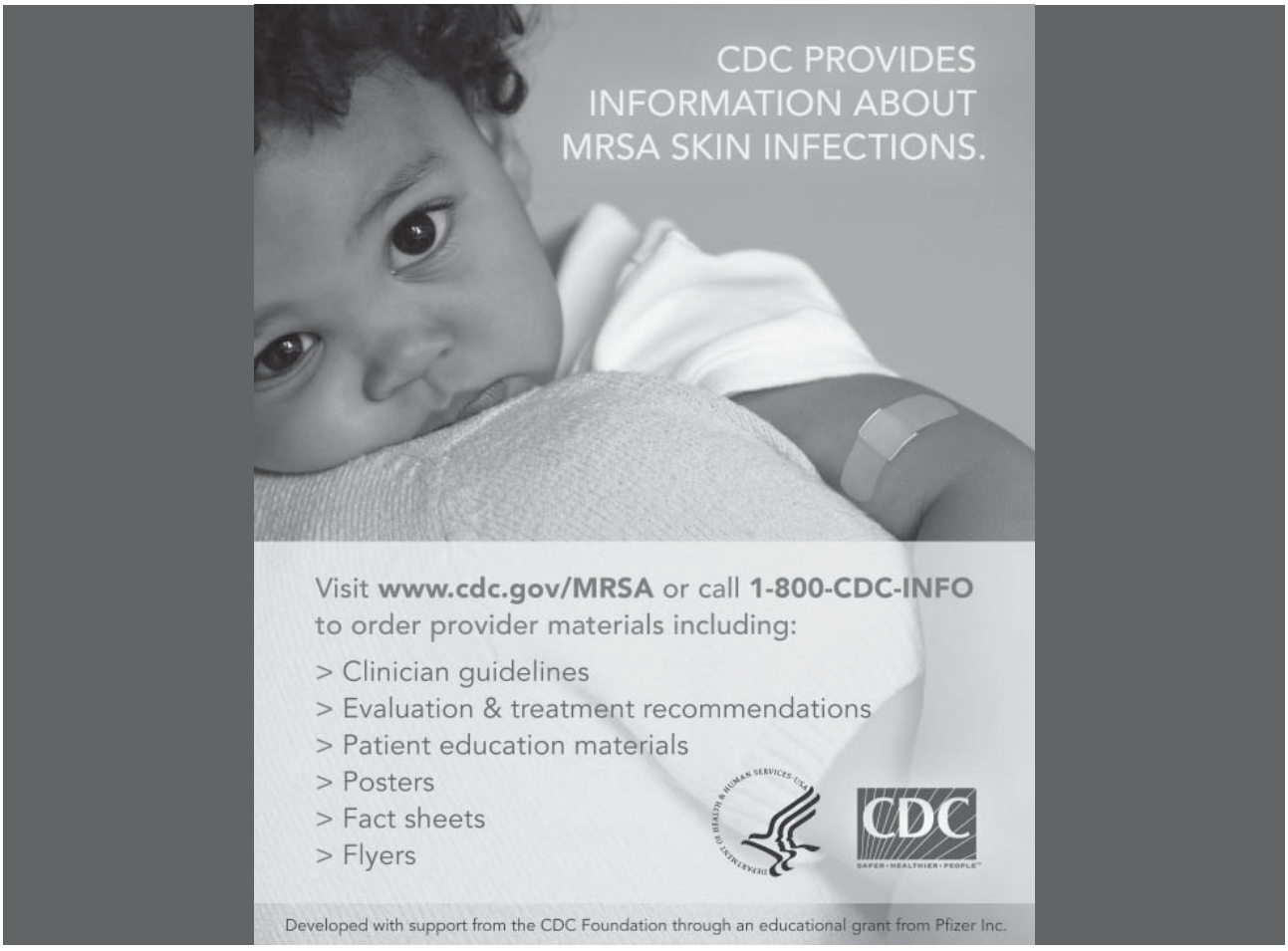

Population Mobility, Globalization, and Antimicrobial Drug Resistance

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Population mobility is a main factor in globalization of public health threats and risks, specifically distribution of antimicrobial drug–resistant organisms. Drug resistance is a major risk in healthcare settings and is emerging as a problem in community-acquired infections. Traditional health policy approaches have focused on diseases of global public health significance such as tuberculosis, yellow fever, and cholera; however, new diseases and resistant organisms challenge existing approaches. Clinical implications and health policy challenges associated with movement of persons across barriers permeable to products, pathogens, and toxins (e.g., geopolitical borders, patient care environments) are complex. Outcomes are complicated by high numbers of persons who move across disparate and diverse settings of disease threat and risk. Existing policies and processes lack design and capacity to prevent or mitigate adverse health outcomes. We propose an approach to global public health risk management that integrates population factors with effective and timely application of policies and processes.

Human mobility is causing an increase in antimicrobial drug–resistant organisms and drug-resistant infectious diseases. International population movement is an integral component of the globalization process. Current population movement dynamics rapidly and effectively link regions of marked health disparity, and these linkages can be associated with risk for importation of drug-resistant infectious diseases.

During the past century, developments in public health sanitation (*1*), infrastructure engineering (*2*), vaccines (*3*), and antimicrobial drugs have contributed substantially to the control of infectious diseases, markedly decreasing associated illness and death. These developments have largely occurred in economically advanced regions and have produced complacency and a belief that the public health threats posed by infectious diseases have been conquered. However, by the early 1990s, infectious diseases were again being identified as substantial domestic and international public health threats in and to western nations (*4*).

Although many infections of clinical relevance are effectively managed with the use of vaccines, antimicrobial drugs, or newer therapies, challenges to the control of infectious diseases remain. These challenges occur in industrialized and in developing countries and result at least in part from the failure of antimicrobial drugs to meet expectations for management and control of disease in clinical and public health contexts. Declining antimicrobial drug effectiveness has current and future consequences that affect all elements of the health sector, e.g., research and development, public health policy, service delivery, and payment programs. The emergence of antimicrobial drug resistance adversely affects patient care and threatens effective management of public health infectious diseases globally (*5*).

Antimicrobial drug failure may occur for many reasons, e.g., reduced adherence to drug therapy, suboptimal dosing, diagnostic and laboratory error, ineffective infection control, counterfeit or altered drugs, and resistance (innate or acquired). Although much attention is focused on resistance patterns of eubacteria (*6*), resistance is being found for virtually all microbial agents including mycobacteria (*7*,*8*), viruses (*9*,*10*), parasites (*11*,*12*), and fungi (*13*,*14*). Antimicrobial drug resistance phenotype is com-

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monly described in terms of the resistance characteristics of the microorganism. These characteristics are either constitutionally based intrinsic characteristics of the organism or resistance factors acquired through induced genetic expression or gene transfer between organisms.

Human activities strongly affect acquired resistance. Emergence of drug resistance in environments that enable sharing of drug-resistance genes between organisms has been documented. Human activities that contribute to ecological niche pressures, such as antimicrobial drug use (*15*) and manufacturing or biological waste disposal into the environment (*16*,*17*), can support the development of resistance.

Against this background of diverse antimicrobial drug resistance, interregional migration and the processes associated with international population mobility can affect the spread and distribution of resistant organisms. These mechanisms of spread become increasingly common when people move among locations with disparate delivery of health services, public health systems, and regulatory frameworks for therapeutic drugs, particularly antimicrobial agents. We describe the role of population mobility in the dispersal of drug-resistant organisms and the emerging need for global standards, programs, and policies in the management of drug resistance, especially for mobile populations.

Population Mobility and Association with Infectious Diseases and Microbial Resistance

Each year, ≈2 billion persons move across large geographic distances; approximately half cross international boundaries (Table). The International Air Transport Association reported that their members carried 1.6 billion passengers in 2007, among which 699 million flew internationally (*24*). The United Nations World Tourism Organization estimated 924 million international tourist arrivals in 2008 (*19*). International movements for permanent resettlement by immigrants, refugees, asylum seekers, or refugee claimants, and temporary movement by migrant workers and others augment the total international movements each year. The International Labour Organization stated that in 2004, an estimated 175 million persons (3% of the world's population) lived permanently outside their country of birth and that there were 81 million migrant workers (excluding refugees) globally (*22*).

Despite the magnitude of mobile populations, translating international movement statistics into imported disease risk is challenging for several reasons. Domestic surveillance systems generally report disease events and only occasionally refer to infection in the context of place of acquisition. Patients' travel or migration history may not be routinely gathered as part of the reporting requirements. Nevertheless, considerable information supports the belief that international population mobility plays a role in introducing antimicrobial drug–resistant disease, as follows.

Human Travel to Disease-Nonendemic or Low Disease–Endemicity Regions

Mobile population importation of drug-resistant infections and diseases is most evident where the expected frequency of the infection or disease is low or absent. For diseases in nonendemic areas, it can be fairly assumed that humans imported the disease. Many examples of imported multidrug-resistant (MDR) infectious diseases are associated with migrant populations, e.g., MDR *Plasmodium falciparum* malaria in immigrants, tourists, and returned foreign-born travelers (*25*–*27*). Tuberculosis in regions of low disease endemicity, such as western Europe and North America, is also related to the influx of persons from tuberculosis-hyperendemic areas (*28*). Tuberculosis in foreign-born persons can shift the local disease epidemiology from endemic to imported and includes the risk for MDR TB (*29*–*32*) and extensively drug-resistant (XDR) TB (*33*,*34*).

Geographic Tracking of Human-to-Human Transmitted Diseases and Drug Resistance over Time

The emergence of high-level resistance to penicillin G by *Streptococcus pneumoniae*, first described in South Africa in 1977, followed by resistance to multiple drugs is an example of international tracking of human-to-human disease and this organism over almost 4 decades. Modern molecular microbiologic techniques are now being used to confirm its global spread (*35*).

Table. Global estimates of annual migrant populations

Administrative category	Population estimates and year	Reference
Refugees	16 million in 2007	(*18*)
Asylum seekers or refugee claimants	650,000 in 2007	(*18*)
Internally displaced persons	51 million in 2007, includes those displaced by natural disasters and conflict	(*18*)
Temporary (recreational or business travel) movement	924 million in 2008	(*19*)
Regular immigrants	Annual flow of 2.4 million, reported in 2005 (from a stock of 200 million immigrants worldwide)	(*20*)
International students	2.1 million in 2003	(*21*)
Migrant workers	81–86 million in 2005	(*22*)
Trafficked (across international borders) persons	Estimated 800,000 in 2006	(*23*)
Domestic arrivals, by air	Estimated 900 million in 2007	(*24*)

Similar studies have been conducted on the international spread of drug-resistant gonorrhea (*36*,*37*). *Neisseria gonorrhoeae* resistant to penicillin, tetracycline, and multiple other drugs, detected in Southeast Asia during the 1960s and 1970s, has been an emerging public health issue in the United States (*38*,*39*). The reported emergence of quinolone-resistant gonorrhea in the United States (*40*) followed a similar pattern of reactive public health response to the contribution of human mobility to international and then intranational spread. Successive treatment guidelines emphasize the importance of population mobility and the dispersal of resistant organisms in this illness (reference 41 in online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1727-Techapp.pdf). The convergence of a resistant threat with decreased access to effective alternative therapy (cefixime shortage) during 2002–2003 complicated management and control (reference 42 in online Technical Appendix). Increasingly, development of clinical management guidelines for diagnosing and treating illness caused by many resistant organisms will refer to international differences in drug-resistance patterns (reference 43 in online Technical Appendix).

Since multidrug– or methicillin–resistant *Staphylococcus aureus* (MRSA) was first reported in the United States in 1968, its prevalence in North American healthcare institutions has grown, contributing to increased (number and duration) hospital stays and an associated increased number and severity of cases and more deaths (references 44,45 in online Technical Appendix). Recent descriptions of primary community-associated MRSA infections causing death have raised concerns about the control and management of this organism in not only North America but other locales worldwide as well (references 46,47 in online Technical Appendix). Clinical and laboratory testing can link distant disease exposures to local isolation of resistant strains (references 48–50 in online Technical Appendix). A worrying development of antimicrobial drug resistance in *S. aureus* has been the emergence and geographic extension of reduced susceptibility to vancomycin, which at one time was the reliable backup therapy for MRSA infections (references 51–53 in online Technical Appendix). Although MRSA is not uniquely a human pathogen, the nature of its clinical distribution and ability to be carried in asymptomatic persons supports its association with human-to-human transmission over large distances.

Humans as Asymptomatic Carriers or Mobile Vectors of Antimicrobial Drug–Resistant Organisms

As with MRSA, humans can asymptomatically carry and transmit other cutaneous, enteric, or respiratory microbial flora from zones of high to low prevalence. Some of these organisms may have innate drug resistance or may reflect acquired resistance patterns that are not typical of locally acquired disease. Typhoid disease, *Shigella,* and *Campylobacter* infections are a few of many other enteric infections for which humans are documented carriers (references 54–56 in online Technical Appendix).

Recently, the potential for drug-resistant influenza viruses with emergent and pandemic potential has captured considerable global health attention (references 57–59 in online Technical Appendix). The local appearance of novel influenza strains with rapid global distribution raises questions about the role of human mobility in the spread and distribution of drug-resistant viruses (reference 60 in online Technical Appendix). Although local antiviral drug pressure is associated with rapid appearance of resistance, drug-resistant strains of influenza have also been associated with importation (reference 61 in online Technical Appendix).

The role of international tourists, travelers, or migrants colonized with antimicrobial drug–resistant organisms, in terms of transmission potential when they arrive in areas of a low disease prevalence, is difficult to detect and largely unexplored (reference 62 in online Technical Appendix). The reality of this risk is illustrated when persons obtain healthcare services outside their normal place of residence. Wounded military personnel and a group often referred to as medical tourists are at increased risk of acquiring nosocomial infections caused by drug-resistant organisms and of subsequently importing their infections when they repatriate to their country of residency.

Additionally, the role of international facilities that provide dental, surgical, medical, diagnostic, and therapeutic services to international travelers is expanding (reference 63 in online Technical Appendix). Health services in other countries may be provided in regulatory and standardization environments that differ from those at the patients' place of origin. The estimated risk for hospital-acquired infections in developing countries is 2–20× greater than that in industrialized countries (reference 64 in online Technical Appendix). Antimicrobial drug–resistance patterns may also differ, as may health services, infection control practices, and public health requirements for surveillance and reporting of antimicrobial drug resistance. The extension and transfer of nosocomial infections between regions and within the community has been well documented at the national level (references 65–67 in online Technical Appendix). As more high-risk and vulnerable populations travel internationally, either requiring or planning medical or surgical care abroad, or as migrants enter countries seeking healthcare services not available in their own countries, the international consequences of imported drug-resistant infections will be seen more frequently.

In some scenarios, linking the emergence of antimicrobial drug resistance and international mobility can be challenging. Given the global prevalence of many com-

mon organisms, their role in causing infections in high-risk populations (e.g., the elderly and patients with concurrent conditions such as diabetes, renal failure, malignancy, or immune compromise or patients who have had abdominal surgery) or certain institutional environments (e.g., intensive care units, burn units, long-term care facilities) may create similar local pressures potentially leading to multifocal emergence of drug resistance. Regardless of whether simultaneous multifocal emergence of resistance is a factor, unaffected areas will be linked to affected areas through mobilization of persons from zones of high to low prevalence. Microbial identification and typing systems, antibiograms, and new technologies for identifying genetic clones and "fingerprints" of microbes are better at defining the origin and patterns of spread of MDR organisms.

Local monitoring of susceptibility patterns combined with knowledge of emerging drug resistance, regionally or internationally, is already recognized as a component of some resistant infections such as MDR TB and XDR TB. Growing population mobility makes local monitoring an increasingly important component of routine surveillance for antimicrobial resistance.

Role of International Policies, Processes, and Globalization in the Control of Imported Antimicrobial Drug–Resistant Diseases

Since development of the first international maritime sanitation regulations in 1832, coordinated international responses have been required to manage common threats. Such undertakings have always had to balance the benefits of mitigation with the negative effects of disease control interventions on international trade and commerce (reference 68 in online Technical Appendix). The modern version of these regulations, the International Health Regulations, focuses on a limited number of diseases and outbreaks of international public health significance for surveillance and reporting but only peripherally addresses population mobility and drug-resistance patterns (reference 69 in online Technical Appendix).

The association of international movements of conveyances, goods, and people with introductions of disease and vectors has been long recognized (references 70–71 in online Technical Appendix). Human travel, trade, and commerce have frequently been implicated in the redistribution of diseases. Examples include yellow fever in the 18th and 19th centuries, anopheline mosquito malaria vectors in the 1930s, and, more recently, *Aedes albopictus* and dengue, the extension of West Nile Virus infection into North America, and the spread of chikungunya infections in Europe (references 72–76 in online Technical Appendix). No specific antimicrobial therapies are available for yellow fever, dengue, West Nile, and chikungunya viruses, among others. Expanding human population mobility will affect and influence the spread, introduction, and endemicity of resistant and untreatable microbes because infections are unequally and rather unpredictably distributed around the world.

Proposed Approach to Global Public Health Risk Management

As recently demonstrated by influenza A pandemic (H1N1) 2009 virus, the volume, rapidity, and complexity of international movements exceed current international disease control practices (reference 77 in online Technical Appendix). Effective responses require engagement of local capacities, standardization of practices, multisectorial partnerships, and rigorous health intelligence with threat and risk assessment. The spread and introduction of resistant infections may not be preventable; but planning, recognition, and coordinated response can mitigate the consequences. Specifically, to control antimicrobial drug resistance and international movement of disease risk associated with human mobility, greater international collaboration and standardization are needed in the following areas:

- Prescriber education, training, and invigilation in terms of antimicrobial drug stewardship for good patient care and reduction of risk for emerging drug resistance.
- Infection control training, certification, and practice.
- Laboratory methods, proficiency testing, and quality management.
- Active and passive surveillance systems, including routine gathering of travel and migration history, rapid analysis, and reporting.
- Engagement of process and regulatory tools unrelated to public health but related to health outcomes, e.g., good manufacturing practices and quality systems for medical devices and pharmaceuticals (references 78,79 in online Technical Appendix).
- Pharmaceutical security systems for standard and quality medicines. (The importance of this issue relevant to drug effectiveness, patient safety, and emergence of resistance appeared in a United States Pharmacopeia drug quality report from countries associated with the US Agency for International Development; the report indicated that antibiotic drugs, antimalarial drugs, antituberculous drugs, and antiretroviral agents for treatment of HIV/AIDS were found to be commonly substandard or counterfeit [reference 80 in online Technical Appendix]. Even in industrialized countries, counterfeit drugs may enter the marketplace either directly from local illegal producers or through international portals such as

importation or Internet pharmacy access [references 81–83 in online Technical Appendix.])

- Animal and plant health sector engagement. (Not only do subtherapeutic, subquality antiinfective therapies and low-level environmental antimicrobial drugs affect illness and death at the human level, but they also have the potential for emergence of drug resistance at the microbial level [references 84–88 in online Technical Appendix.])

Although all the above-listed efforts are essential, none will be sufficient without integrating the role played by humans and their international movement into modeling the complex relationship with antimicrobial drug resistance and microorganisms (reference 89 in online Technical Appendix). Enhanced global surveillance and population mapping demarcating differential zones of disease prevalence and major health disparities will support targeted interventions such as routine drug sensitivity analyses for infections originating in certain situations.

Acknowledging the dynamic role of population mobility in emerging risks to public health is a first step in formulating an effective response, but other components will be needed if this risk is to be successfully mitigated (reference 90 in online Technical Appendix). Components of this response will include the following:

- Accurate and robust assessment of threat to risk management based on modern population characteristics that include mobility, travel, and migration history.
- Mitigation of risk through nonhealth partnerships in other sectors, including economics and trade, education, agriculture, and security, all of which will affect the determinants of health, regional disease outcomes, and critical decision making for effective intervention and control.
- Augmenting local knowledge and timely communications related to populations expressing emerging disease threats and risks and linking early detection through diagnostic and confirmatory epidemiologic tools and medical technology.

Conclusions

Although the association of human movement with antimicrobial drug resistance is not new, the extent of risk to public health caused by population mobility and drug-resistant infections is increasing. A shift in the existing paradigm of pathogen-focused policies and programs would contribute to a healthier future for everyone. The shift should address population mobility as a part of an integrated approach to decrease globalization of infectious disease threats and risks.

Dr MacPherson is a clinician, laboratorian, researcher, and advisor to multiple governments and agencies on population health issues. His primary interest is advocating for "people first" in all aspects of medicine.

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Public Health Response to Imported Case of Poliomyelitis, Australia, 2007

John A. Carnie, Rosemary Lester, Rodney Moran, Lynne Brown, Julian Meagher, Jason A. Roberts, and Bruce R. Thorley

Australia, along with 36 other countries in the Western Pacific Region, was declared free of poliomyelitis by the World Health Organization in October 2000. Yet, the persistence of wild poliovirus in the 4 remaining polio-endemic countries—Afghanistan, India, Nigeria, and Pakistan—poses a risk for its importation into all countries declared polio free. We describe the public health response and outcomes resulting from the importation of a wild poliovirus infection in Melbourne, Australia, in July 2007. This response, based on an assessment of the risk for transmission, included offering vaccination with inactivated polio vaccine to the contacts and placing the index patient in isolation and the household contacts in quarantine until consecutive fecal specimens were negative for poliovirus by culture. The experience gained from the polio importation event in Australia may assist other polio-free countries to prepare for, and respond to, a similar event. No secondary clinical cases resulted from this importation.

Since 2006, wild poliovirus has been endemic in only 4 countries: Afghanistan, India, Nigeria, and Pakistan. Although many countries have not reported a case of poliomyelitis caused by wild poliovirus for some years, they remain at risk for importation of the disease. Australia and the other countries of the Western Pacific Region were declared polio free in October 2000 (*1*). However, the last reported case of wild poliovirus infection in Australia was imported from Turkey in 1977 (*2*). National departments of health in this region must remain vigilant for such an event and respond appropriately to reduce the risk for local transmission.

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The World Health Organization (WHO) Global Polio Eradication Initiative recommends clinical surveillance for cases of acute flaccid paralysis in children <15 years of age and suspected paralytic polio in a person of any age as the most sensitive means of detecting a case of imported poliomyelitis in countries declared polio free (*3*). The Australian government initiated surveillance for acute flaccid paralysis, following the WHO guidelines, in 1995. WHO established a global polio laboratory network, which includes a Polio Regional Reference Laboratory in Australia, to confirm poliovirus infection because other conditions manifesting acute paralysis can mimic polio. Nevertheless, Australia's ability to detect and respond effectively to the importation of a wild poliovirus infection has been questioned because gaps have occurred in surveillance for acute flaccid paralysis surveillance and in the referral of fecal specimens for laboratory testing (*4*).

Australia began exclusive use of inactivated polio vaccine (IPV) in place of the Sabin oral polio vaccine on November 1, 2005. In Victoria in 2007, the proportion of children who received at least 3 doses of polio vaccine was 92.8% at 12 months of age and 95.9% at 2 years of age. Coverage with at least 4 doses of polio vaccine was 91.4% at 6 years of age. No reliable data exist on vaccination coverage with polio vaccine in the adult population.

We describe the public health response to an importation of wild poliovirus infection that occurred in Melbourne, Australia, in July 2007; the last reported case of polio in Australia was in 1977 (*2*). The issues addressed as a result of this event would be similar for other countries, and the lessons learned may be incorporated into national planning for a polio outbreak (which requires only a single confirmed case).

Notification of the Index Case

On July 7, 2007, the Department of Human Services (DHS) in Victoria, Australia, was notified of a suspected

case of imported poliomyelitis in a 22-year-old man (a university student). The patient, who was studying in Melbourne, had returned home to Pakistan on March 13, 2007, and in early June, he visited Islamabad and the North-West Frontier Province. On June 22, 2007, fever, nausea, and pain in the lower back and legs developed and progressed to lower limb weakness. The symptoms appeared to resolve, and he returned to Melbourne, arriving on a flight from Bangkok, Thailand, on July 2, 2007. However, he remained at home with back pain and lower limb weakness and consulted a general practitioner on July 6, 2007. He was advised to go to a hospital, where the emergency department admitted him for further investigation. The patient reported receiving at least 3 doses of oral poliomyelitis vaccine as a child.

A case report describing the clinical features and treatment of the patient and the initial laboratory investigation was published by Stewardson et al. (*5*). Briefly, a magnetic resonance image of the patient's spine, performed on July 7, indicated increased signal in the anterior horn cells, which is highly suggestive of poliomyelitis. The patient was placed in a single room with enteric precautions, and DHS was notified of the diagnosis of poliomyelitis. Although an initial pan-enterovirus reverse transcription–PCR (RT-PCR) performed directly on a fecal specimen collected on July 7 was reported as negative, the National Polio Reference Laboratory confirmed the diagnosis of poliomyelitis by isolation of non–Sabin-like poliovirus type 1 on July 13. The virus was subsequently reported to have high nucleic acid sequence identity with wild poliovirus isolates from Pakistan, which provided an epidemiologic link with the patient's travel history. The index patient was placed in isolation in the hospital until 2 successive fecal specimens, collected 1 week apart, were negative for poliovirus by viral culture and RT-PCR (a total of 34 days).

Public Health Response

DHS coordinated the public health response in the state of Victoria, while national and international responsibilities were handled by the Australian government Department of Health and Ageing. At the national level, this included liaising with the Communicable Diseases Network of Australia, the Australian Health Protection Committee, and the Public Health Laboratory Network. The case was one of the first reported to WHO under the International Health Regulations (2005), which came into effect in June 2007 and require member countries to notify WHO of poliomyelitis cases (*6*). On confirmation of the diagnosis of poliomyelitis, DHS performed a risk assessment for the potential infection of contacts of the index patient with wild poliovirus. Contacts were grouped as the following: 1) close contacts who resided with or visited the index patient's residence, 2) fellow passengers on the airplane from Bangkok to Melbourne, 3) public contacts and staff at the general practitioner's clinic, and 4) public contacts and healthcare workers (HCWs) at the hospital (Table 1).

Household contacts were judged to be at highest risk. Anyone who used the same toilet as the index patient before it had been cleaned was regarded as being at lesser risk, especially because the patient had not used a toilet to have a bowel movement either on the plane, at the general practitioner's clinic, or at the hospital emergency department. In virtually all instances, the vaccination history of contacts was uncertain. Although the likelihood of transmission was deemed to be low, a cautious approach to the situation led to a comprehensive public health response.

Household Contacts

Household contacts of the index patient were identified as his 5 housemates, 1 visitor who had stayed overnight after the index patient's return from overseas, and a housekeeper who cleaned the index-patient's premises, but did not reside there. The household contacts were placed under a public health order following the state's health laws to remain in home quarantine until released by DHS. The 5 housemates were quarantined at their principal place of residence, together with the visitor who joined them. The housekeeper was quarantined in her own house. The contacts were provided with information on poliomyelitis and given booster doses of IPV. Doses of IPV were administered subcutaneously, according to the Australian immunization guidelines (*7*), thus avoiding the potential for provocation poliomyelitis (*8*). In hindsight, serum collection from close contacts before booster vaccination would have enabled testing for immunoglobulin M against poliovirus to assess the risk for transmission of wild poliovirus due to asymptomatic infection. All household contacts remained in quarantine until 2 fecal specimens, collected >24 hours apart, were negative by viral culture and RT-PCR (a total of 16 days) (Table 1).

Airplane Contacts

The index patient reported that he had used the toilet on the flight from Bangkok to Melbourne, although only to urinate. Although the risk to the fellow passengers was deemed to be low, contact tracing was instituted for the passengers on the flight. Two hundred thirty-five passengers terminated their journey in Melbourne (a few passengers went on to other areas in Australia), and their incoming passenger cards were obtained by DHS through the Department of Health and Ageing. Upon laboratory confirmation of the diagnosis of the traveler's poliomyelitis, a media bulletin was released by DHS on July 14, advising the public of the case and asking passengers from the flight to contact a national public health telephone

Table 1. Summary of the public health response and the outcomes to the importation of wild poliovirus, Australia, July 2007*

Persons investigated	Response	Outcome
Index patient	Isolated in hospital after magnetic resonance image was suggestive of poliomyelitis.	Discharged when 2 fecal specimens, collected at least 7 d apart, were negative for enterovirus by cell culture and RT-PCR (total of 34 d).
Household contacts	5 housemates, 1 visitor, and the housekeeper received IPV and placed in home quarantine under a Public Health Order. Recommend serum collection before vaccinating contacts to test for IgM against polio. Another friend who visited the residence of the index case was boosted with IPV only.	Home quarantine lifted when 2 fecal specimens, collected 24–48 h apart, were negative for enterovirus by cell culture and RT-PCR. Housemates required support to ensure compliance, which included grocery deliveries, bill payments, and a range of other assistance.
Airplane contacts	Media release informing public of imported case of polio and offer of vaccination for persons who disembarked in Melbourne. DHS provided with 235 Passenger Declaration cards of persons who disembarked in Melbourne. DHS undertook contact tracing of airplane passengers (Table 2). One teenage passenger hospitalized with fever and diarrhea. 10 persons not on the airplane manifest were vaccinated as their details could not be readily determined; 7 airport workers who cleaned the plane were vaccinated with IPV.	Hospitalized passenger: single CSF and 3 fecal specimens (collected more than 24 h apart), were tested for enterovirus; CSF positive for enterovirus RNA by RT-PCR; all other tests negative by cell culture and RT-PCR.
Medical clinic contacts	14 staff members and 81 patients initially regarded as potentially at risk for exposure. Nine staff identified as at risk and offered vaccination with IPV. 24 patients and 6 relatives/friends identified as at risk and offered vaccination with IPV. Letters sent to a further 8 recommending vaccination. Adult patient later hospitalized with fever, gastrointestinal illness and general weakness and spouse had respiratory illness. Upon discharge, they were asked to remain at home pending specimen results. 7-y-old child was later hospitalized with seizures.	Adult admitted to hospital and spouse: 2 fecal specimens, collected more than 24 h apart, negative for enterovirus by cell culture and RT-PCR. Child who was hospitalized: 1 CSF and a fecal specimen tested for enterovirus; CSF positive for enterovirus RNA by RT-PCR, fecal specimen negative for enterovirus by RT-PCR and cell culture.
Contacts at Box Hill Hospital	102 patients and 63 relatives/friends from either the Emergency Department or the Ward were identified as at risk: 17 were not contactable; 37 were vaccinated by their own doctors; 83 HCWs were identified as at risk and vaccinated with IPV. Identification of 9 overseas-born HCWs without evidence of recent polio vaccination.	Symptomatic HCW with back pain: single fecal specimen negative for enterovirus by RT-PCR and cell culture. HCWs without evidence of recent polio vaccination: 2 fecal specimens, collected more than 24 h apart, negative for enterovirus by RT-PCR and cell culture.

*IPV, inactivated polio vaccine; RT-PCR, reverse transcription–PCR; Ig, immunoglobulin; CSF, cerebrospinal fluid; HCW, healthcare worker.

line to obtain further information and to receive a booster polio vaccination. Media interviews were conducted by DHS staff, and a health alert was issued for hospitals in Victoria.

DHS also contacted the airplane passengers directly by telephone, letter, or email to provide information on poliomyelitis and offer a single booster dose of IPV, regardless of previous poliomyelitis vaccination history. The results of the airplane contact tracing are shown in Table 2. Seven airport workers responsible for cleaning the plane used by the index patient were also given IPV by DHS, while the Department of Health and Ageing agreed to undertake follow-up of the flight crew.

Contacts at the Medical Clinic

On July 6, 2007, the index patient consulted a general practitioner about the symptoms that recurred after his arrival in Melbourne on July 2. He later informed DHS that he had used a toilet at the clinic to pass urine only and so the same risk assessment criteria were used as for the airplane contacts. Nine healthcare staff, 24 patients, and 6 of their friends or relatives were administered IPV.

Hospital Contacts

We identified persons who may have used a toilet at the hospital Emergency Department and on the ward where the index patient stayed before isolation procedures were instituted, and we recommended that they receive IPV (Table 1). In total, 37 hospital patients or their friends or relatives were administered IPV by their own doctors, and 3 had recently received their routine childhood vaccinations.

HCWs who possibly had contact with the index patient were regarded as at risk, and a total of 83 hospital staff members each received 1 dose of IPV. Australian-born HCWs were judged likely to have been fully immunized and therefore less likely to be at risk. Nine overseas-born hospital staff members who could not provide evidence of vaccination or a booster dose within the last 10 years, per the Australian immunization guidelines (*7*), were requested to provide 2 fecal specimens, at least 24 hours apart, for virus culture.

Table 2. Outcome of tracing the 235 airline passengers who arrived in Melbourne, Australia, on the same flight as the index patient with polio, 2007*

Action	No. passengers
Vaccinated with IPV by DHS	77
Preferred vaccination by own doctor	96
Refused vaccination	4
Recently vaccinated against polio	3
Contacted by letter	14
Contacted by email	15
Subtotal	209
Incorrect email or mail address	12
Illegible incoming passenger cards	14

*IPV, inactivated polio vaccine; DHS, Department of Health Services.

Symptomatic Contacts

Three symptomatic cases that required hospitalization were identified during contact tracing (Table 1). A teenager on the same flight from Bangkok as the index patient was hospitalized with fever and diarrhea, and a 7-year-old child who attended the same general practitioner's clinic as the index patient was admitted with seizures. Cerebrospinal fluid (CSF) collected from both patients was positive for enterovirus RNA by RT-PCR, but fecal specimens were negative by cell culture and RT-PCR. The enteroviruses detected in the CSF from both patients were not identified. In addition, a man who attended the general practitioner's clinic was hospitalized with fever, gastrointestinal illness, and general weakness. Two fecal specimens were collected from the patient and also from his spouse, who was having a respiratory illness, as a precautionary measure. The couple was asked to remain at home in voluntary quarantine until laboratory testing of the specimens was completed. All fecal specimens were reported as negative for enterovirus by cell culture and RT-PCR. One hospital HCW who had contact with the index patient exhibited backache, but a fecal specimen was negative for enterovirus by RT-PCR and cell culture.

Cleaning and Disinfection

Lastly, the issue arose of cleaning and disinfection of toilets used by the index patient. Survival of poliovirus is favored by lower temperatures and high relative humidity. The virus can survive outside the human body for weeks at room temperature (*9*). Effective disinfectants include sodium hypochlorite, glutaraldehyde, or formaldehyde solutions. The WHO Guide to Hygiene and Sanitation in Aviation (*10*) indicates that the correct use of sodium hypochlorite is to apply a solution of 100 mg/L and keep it in contact with surfaces for 30 minutes; then the surfaces should be rinsed with warm water and dried.

Discussion

The 2007 wild poliovirus importation generated widespread media coverage around Australia that assisted with contact tracing. However, tracing the passengers who disembarked with the index patient in Melbourne was difficult because of poor handwriting and inaccurate information on many of the arrival cards. This experience has implications for the urgent tracing of persons potentially exposed to other infectious diseases of public health significance, such as pandemic influenza. Despite extensive contact tracing, 26 (11%) of the 235 passengers could not be contacted. For the 96 passengers who chose to see their own doctor for vaccination and the 29 passengers who were contacted by letter or email, outcome is not known.

In large part, the laboratory investigation of the index patient and household contacts followed the procedures recommended by WHO for routine acute flaccid paralysis surveillance with collection of 2 fecal specimens obtained 24–48 hours apart, due to intermittent virus shedding, for virus culture (*11*). Virus cell culture was accepted by DHS as the approved standard for the test procedures, in agreement with the recommendation by WHO. This proved decisive because, for the first fecal specimen, enterovirus was not detected by RT-PCR performed directly on the specimen (*5*). RT-PCR is still a powerful tool for enterovirus detection as exemplified by the test results for the 2 positive CSF specimens. The testing, by cell culture and RT-PCR, of specimens from persons with suspected poliomyelitis and their contacts is recommended. This ensures that test results are determined by using the most rapid and sensitive methods available.

Household contacts of case-patients are at high risk of infection (*12*). We recommended that they be quarantined at home and that stool specimens be collected a minimum of 3 days after the first contact with the index patient to allow sufficient time for an infection to become established. As excretion of poliovirus in the feces can continue for several weeks (*13*,*14*), we sought advice from WHO and the Centers for Disease Control and Prevention (Atlanta, GA, USA) regarding when the index patient and the household contacts could be released from isolation and home quarantine, respectively. The criteria accepted by DHS was for 2 fecal specimens, collected 7 days apart for the index patient and >24 hours apart for the household contacts, to be negative for poliovirus isolation by cell culture (M. Pallansch, S. Roesel, pers. comm.).

The time taken to determine a negative result by cell culture leads to an inevitable delay in finalizing patient tests, which, in the circumstances described in this report, had implications for when the index patient and household contacts could be released from hospital isolation and home quarantine, respectively: 34 days for the index patient and 16 days for the household contacts. It should be noted that household quarantine of the contacts required substantial logistical support by DHS staff in terms of food and entertainment. This also has implica-

tions for large-scale quarantine as would be required in an influenza pandemic.

No published evidence is available on the role of polio vaccine as postexposure prophylaxis against paralytic disease. However, in persons with some preexisting immunity, which would include most of the Australian population, boosting the immune response with a single dose of oral polio vaccine or IPV is likely to reduce both pharyngeal and intestinal excretion of poliovirus in those who have been infected (*15*). The extent to which one undertakes tracing of contacts who used the same toilet was extensively debated by the Communicable Diseases Network Australia and the Australian Health Protection Committee. DHS opted to invite nonhousehold contacts to come to departmental offices or see their own physician for a booster dose of IPV and to be given information on the disease and its symptoms and signs as a precautionary measure. Booster doses of IPV have also been recommended for HCWs who have close contact with patients who might be excreting wild poliovirus (*15*). We followed this advice with the HCWs involved with the index patient, but issues arose in relation to the lack of immunization records, particularly with some of the overseas-born HCWs. We now advise that HCWs in close contact with an index patient with poliomyelitis, who have no recorded immunization history or who are not fully vaccinated, should provide 2 fecal specimens collected 24–48 hours apart and complete a course of vaccination with IPV, in accordance with the current Australian immunization guidelines (*7*).

Conclusions

Until this imported case, poliomyelitis caused by wild poliovirus had not been reported in Australia for 30 years. The case necessitated a rapid and extensive public health response. The age and vaccination history of the index patient highlight the need for public health officials worldwide to prepare for imported cases of suspected polio in persons of any age and with prior vaccination. The experience gained from the public health response to the importation in 2007, particularly in relation to tracing of contacts, isolation of cases, and quarantine of close contacts, has been incorporated into the national outbreak response plan for the investigation of cases of acute flaccid paralysis and suspected polio, published by the Australian government's Department of Health and Ageing (*16*).

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Hepatitis E Outbreak on Cruise Ship

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In 2008, acute hepatitis E infection was confirmed in 4 passengers returning to the United Kingdom after a world cruise. Epidemiologic investigation showed that of 789 persons who provided blood samples, 195 (25%) were seropositive, 33 (4%) had immunoglobulin [Ig] M levels consistent with recent acute infection (11 of these persons were symptomatic), and 162 (21%) had IgG only, consistent with past infection. Passenger mean age was 68 years. Most (426/789, 54%) passengers were female, yet most with acute infection (25/33, 76%) were male. Sequencing of RNA from 3 case-patients identified hepatitis E virus genotype 3, closely homologous to genotype 3 viruses from Europe. Significant association with acute infection was found for being male, drinking alcohol, and consuming shellfish while on board (odds ratio 4.27, 95% confidence interval 1.23–26.94, p = 0.019). This was probably a common-source foodborne outbreak.

In 1980, hepatitis E virus (HEV) was recognized as a cause of human disease (*1*,*2*). HEV infections can be asymptomatic or they can induce clinical hepatitis, which may be severe or life threatening, particularly for pregnant women. Other clinical manifestations associated with HEV infection have been reported. HEV is usually transmitted by the fecal–oral route and has an incubation period of 15–60 days (*3*). Four HEV genotypes that infect humans have been identified: genotype 1 is regularly found in HEV-endemic areas such as Africa and Asia; genotype 2 in Mexico and West Africa; genotype 3 in the United States, Europe, and Japan; and genotype 4 in Asia (*3*,*4*). Although HEV is increasingly recognized as a cause of hepatitis in industrialized countries (*5*,*6*), it is thought to be a relatively uncommon cause of viral hepatitis in the United Kingdom.

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On March 27, 2008, the Southampton Port Health Authority informed the Health Protection Agency (HPA) of 4 elderly ship passengers with jaundice, who were returning from a world cruise. Because they had been fully vaccinated against hepatitis A, HEV was considered and subsequently identified as the probable causative agent. The ship had departed from Southampton, UK, on January 7 and returned on March 28, 2008. The ship had sequentially visited ports in Madeira, the Americas (South, Central, and North), the Caribbean region, Samoa, Tonga, New Zealand, Australia, Hong Kong, Thailand, Singapore, Malaysia, India, Egypt, Greece, and Spain before returning to the United Kingdom. Although the ship had only 1,800 passenger berths (cruise ship company data), the cumulative total of passengers during the cruise approached 3,000 because persons joined and left at different ports.

Because the outbreak of HEV was unusual, especially because it occurred on a cruise ship, and had potential public health implications, an epidemiologic investigation was undertaken. The investigation aimed to identify additional cases, help prevent future incidents by identifying possible risk factors for infection, describe the outbreak epidemiology, and further scientific understanding of the epidemiology and natural history of hepatitis E infection. The investigation was approved and commissioned by the HPA's Hepatitis Programme Board. All participants had been passengers on board the cruise ship and volunteered and gave written informed consent. Ethics approval was not required.

Methods

The investigation focused on all UK passengers who had been on the cruise at any point from January through March 2008. Contact addresses were provided by the cruise ship company, and 2,850 passengers were sent letters inviting them to participate in the investigation and explaining why. On the basis of when they were most likely to have been exposed (ascertained from the first 4 cases), partici-

[1]Other team members are listed at the end of this article.

pants were asked to go to their own doctors to give blood samples within 2 weeks (the time frame for detection of immunoglobulin [Ig] M). HPA provided sample kits with prepaid return packaging. Blood samples were tested for HEV antibodies (IgG and IgM) by using the Fortress Diagnostics ELISAs (Fortress Diagnostics Limited, Antrim, Northern Ireland) at the Virus Reference Department at the HPA Centre for Infections. Assays were run in accordance with the manufacturer's instructions. The Fortress assays were chosen for this investigation because our validation exercises (data not shown) had demonstrated these assays to be more sensitive and specific than some other commercially available assays. Samples were screened for IgG, and those that were positive were then tested for IgM. The IgM-seropositive samples were further analyzed for HEV RNA, and those that were RNA positive were genotyped as previously described (*7*). Briefly, phylogenetic analysis of a 300-bp region of open reading frame 2 was conducted. The generated sequences were compared with genotype 3 sequences from the United Kingdom, Europe, and the United States and with genotype 1, 2, and 4 sequences retrieved from GenBank.

Participants returned self-completed questionnaires by mail. Detailed information was collected about demographic characteristics, potential risk factors and cofactors for disease (medical conditions, food and drink consumption, excursions, water exposure such as water activities in pools on the cruise ship and swimming in the sea while off the ship) and any relevant signs and symptoms. All HPA documents and files containing patient identifiable information were handled and stored in compliance with Caldicott guidance (*8*).

Participants were classified according to their serologic results as having had recent acute infection (serologically confirmed by HEV IgM and IgG), past infection (serologically confirmed by HEV IgG only and therefore unlikely to have been acquired during the cruise), or no infection (serologically negative for HEV IgG). Those with recent acute infection also provided further blood samples for liver function testing and confirmatory HEV antibody testing. Patients with acute cases were followed up by the local Health Protection Unit of the HPA. Liver function tests were performed by local services, and results were reported back to the HPA on a specific form. Blood samples for HEV testing were returned by mail as described above. A symptomatic hepatitis case was defined as recent acute infection in a patient with signs and symptoms compatible with HEV infection, e.g., jaundice and/or dark urine and pale feces. To ensure no false-positive results, additional testing was conducted on samples taken at least 1 month later from these IgM-seropositive participants.

We compared risk factors and exposure for those with recent acute infection with those for seronegative controls. Persons who had evidence of past infection were excluded because they had probably been immune during the study period. Single and multivariable logistic regression, using Stata statistical software, release 10.1 (StataCorp, College Station, TX, USA), was performed to identify the most likely cause of the outbreak and to estimate time and place of exposure. Specific exposures with estimated odds ratios (ORs) >1, $p<0.2$, and at least 50% of cases of recent acute HEV infection, were included in a multivariable model. The least significant factor was dropped from the model in a stepwise fashion until all remaining exposures exhibited a significant association: $p<0.05$ and OR >1.

After the multivariable model was finalized, we added each port visited, 1 at a time, to identify where participants may have been exposed to HEV. The interaction between food item and location was also considered by using a stricter selection criterion of significance level $p<0.01$.

Results

Of the 2,850 passengers, >1,100 volunteered and 851 (30%) participated in the investigation (Figure). Blood samples and questionnaires were available from 659 partic-

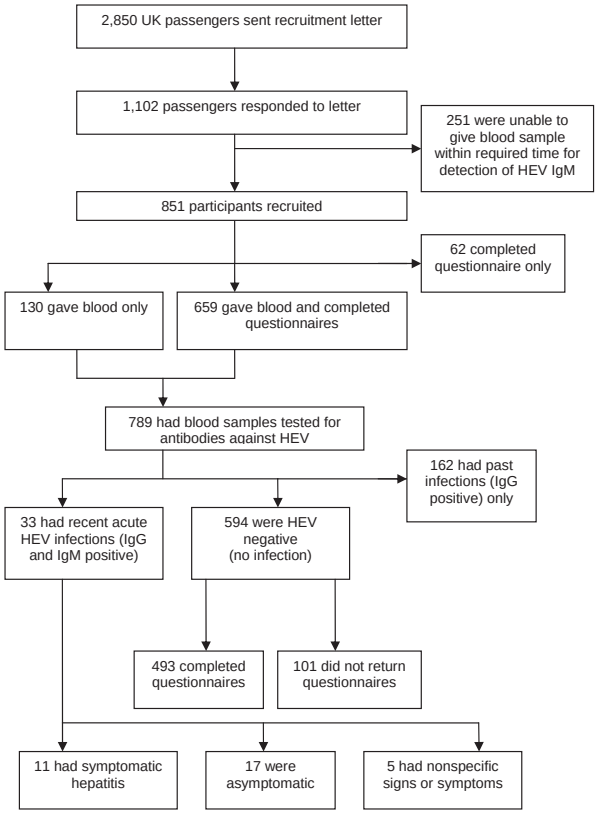

Figure. Recruitment of study participants from among UK passengers on world cruise with hepatitis E outbreak, 2008, and outcomes of epidemiologic investigation and clinical study. HEV, hepatitis E; Ig, immunoglobulin.

ipants. Of these 659, age range was 22–92 years old (mean age 68 years); >90% participants were 55–79 years of age. Of 789 participants who gave blood samples, 426 (54%) were female and 363 (46%) were male.

Laboratory

Including the 4 case-patients identified on the cruise, 33 (4%) participants were classified as having had recent acute infections. A fall in IgM titer with a rise in IgG titer in the second sample collected 1 month later confirmed the acute infections. Another 162 (21%) were classified as having had past infection and 594 (75%) as having had no infection (Figure). Genotyping of RNA sequences obtained from 3 case-patients found genotype 3 virus with sequence homology close to that of other genotype 3 viruses reported throughout Europe.

Statistical Analyses

Univariate analysis showed no statistical association between acute HEV infection and age group (Table 1). Infection was associated with gender; women were less likely than men to have been infected during the cruise. Some evidence indicated association with alcohol consumption; all nondrinkers were HEV negative, and those who drank alcohol (past or present) were more likely to have been infected. Alcohol was consumed by ≈84% of participants, 11% of whom exceeded the recommended weekly intake (defined as a maximum weekly intake of 21 units for men and 14 units for women). Medical conditions, including liver disease, did not appear to be significant risk factors.

Odds of becoming infected were higher for passengers who had embarked from Southampton than for passengers who had joined the cruise at other ports ($p<0.001$). No evidence of association with recent HEV infection was found at any of the ports visited. Of those exposures ashore within the risk period, only excursions in Honolulu, Hawaii, USA (OR 2.22, 95% confidence interval [CI] 0.89–5.49, p = 0.086), and Pago Pago, Samoa (OR 3.26, 95% CI 1.41–7.53, p = 0.006), were significantly associated with infection.

Of the potential exposures on board, univariate analysis showed the following to be significantly associated with infection: unpasteurized cheese, paté, venison, and shellfish (Table 2). When shellfish were further differentiated (prawns, lobster, crab, mussels, scallops), the association appeared to be significant for lobster and crab; however, few HEV-positive participants said that they had eaten lobster (n = 9) or crab (n = 4). The final multivariable model (Table 3) showed the following to be associated with HEV infection: being male, drinking alcohol, and eating shellfish while on board.

Recent Acute Infections

Of the 33 participants who had had recent acute infections, 25 (76%) were men 57–87 years of age (mean 68 years), and most (76%) were taking medication. All had drunk alcohol, 7 (21%) of whom had exceeded the recommended weekly units. Only 11 had symptoms compatible with hepatitis; 22 (67%) had either no symptoms or nonspecific symptoms of a cold (Figure). Age, gender distribution, and the proportion receiving medication were similar among those who were symptomatic (8 [73%] were male, average age 68 years; 8 [73%] were taking medication) or asymptomatic (13 [76%] were male, average age 69 years; 12 [71%] were taking medication). However, 4 (36%) symptomatic participants had consumed excess alcohol compared with only 1 (6%) asymptomatic participant.

Symptom onset was during March 6–24 (mode March 8, median March 12). Of the 11 symptomatic passengers, 5 had visited the ship's doctor 3–5 days after symptom onset, 3 had been hospitalized, and 6 reported having been sick for 6–21 days (median 12 days).

Table 1. Univariate analysis of probability of having recent acute HEV infection, world cruise ship passengers, 2008, by participant characteristics*

Characteristic	HEV negative	HEV positive	OR	95% CI	p value
Age group, y (n = 526)					
<70	283	18	1.00	Baseline	
≥70	210	15	1.12	0.55–2.28	0.749†
Gender (n = 526)					
M	224	25	1.00	Baseline	
F	269	8	0.31	0.14–0.69	0.002†
Past or present alcohol consumption (n = 523)					
No	49	0	1.00	Baseline	49
Yes	442	32	5.01	0.87–‡	0.061§
Amount of alcohol consumed (n = 415)					
Below recommended	349	23	1.00	Baseline	
Above recommended	37	6	2.46	0.97–6.26	0.058†

*HEV, hepatitis E virus; OR, odds ratio; CI, confidence interval. n values indicate number of responses received in each category.
†χ^2 test.
‡No upper limit.
§Fisher exact test.

Table 2. Univariate analysis of probability of having recent acute HEV infection, world cruise ship passengers, 2008, by potential exposures on board ship*

Exposure	HEV negative	HEV positive	OR	95% CI	p value
Ate shellfish (n = 499)					
No	113	2	1.00	Baseline	
Yes	356	28	4.44	1.17–16.83	0.025†
Ate lobster (n = 319)					
No	263	9	1.00	Baseline	
Yes	38	9	6.92	2.89–16.58	<0.001‡
Ate crab (n = 320)					
No	283	14	1.00	Baseline	
Yes	19	4	4.26	1.39–13.02	0.011‡
Ate shellfish in restaurant A (n = 263)					
No	187	7	1.00	Baseline	
Yes	63	6	2.54	0.85–7.61	0.094‡
Ate bacon (n = 497)					
No	75	1	1.00	Baseline	
Yes	392	29	5.55	0.93–33.25	0.067†
Ate cured pork (n = 454)					
No	272	14	1.00	Baseline	
Yes	154	14	1.77	0.83–3.77	0.141‡
Ate paté (n = 434)					
No	260	9	1.00	Baseline	
Yes	151	14	2.68	1.16–6.16	0.020†
Ate eggs (n = 499)					
No	39	0	1.00	Baseline	
Yes	430	30		Not estimable	0.155‡
Ate unpasteurized cheese (n = 465)					
No	194	7	1.00	Baseline	
Yes	240	24	2.77	1.21–6.37	0.016†
Ate venison (n = 451)					
No	326	17	1.00	Baseline	
Yes	96	12	2.40	1.13–5.10	0.023†
Swam in pool C (n = 494)					
No	336	16	1.00	Baseline	
Yes	130	12	1.94	0.9–4.16	0.089†
Participated in any water activities (n = 493)					
No	210	8	1.00	Baseline	
Yes	254	21	2.17	0.96–4.92	0.063†

*HEV, hepatitis E virus; CI, confidence interval. n values indicate number of responses received in each category.
†χ^2 test.
‡Fisher exact test.

Of the 11 (33%) participants who met the case definition for symptomatic hepatitis, all had loss of appetite, malaise, dark urine, and nausea. Other signs were jaundice and vomiting (n = 7); abdominal pain or discomfort or pale stools (n = 5); and headache, weakness, shakiness, joint pain, rash, or depression. Weeks later, a second phase of illness was reported by 2 participants; both experienced abdominal pain or discomfort, and 1 also had dark urine and lethargy. Blood test results for bilirubin, alanine aminotransferase, alkaline phosphatase, and albumin were available for 10 of 11 participants with symptomatic hepatitis. Levels >2× the expected maximum were found for bilirubin (n = 6), alanine aminotransferase (n = 5), and alkaline phosphatase (n = 2). Aspartate aminotransferase levels were reported for only 3 participants with symptomatic hepatitis and were elevated for 2. Subsequent testing for 2 case-patients showed that liver function had returned to within reference limits. Liver function test results were also reported for 14 of 22 participants who did not have symptomatic hepatitis; none were appreciably elevated. Blood samples from this group were taken later than for those with symptomatic hepatitis, so the possibility of abnormal liver function in the earlier phase of infection cannot be excluded.

Exposure Period and Potential Source of Infection

Our analysis suggests that passengers were at higher risk for HEV infection if they were on the cruise from January 7, when the ship left Southampton, until February 14, when it arrived in Sydney. Most of those with recent acute HEV infection had embarked (January 7) and disembarked

Table 3. Multivariable analysis model of probability of having recent acute HEV infection, world cruise ship, 2008*

Exposure (n = 490)	OR	Profile likelihood, 95% CI	p value
Gender			
F	1.00	Baseline	
M	2.38	1.07–5.68	0.033
Age group			
<70	1.00	Baseline	
≥70	0.96	0.97–1.08	0.384
Medication taken			
No	1.00	Baseline	
Yes	1.65	0.68–4.62	0.282
Any past or present alcohol consumption			
No	1.00	Baseline	
Yes		Not estimable	0.033
Shellfish consumed on board			
No	1.00	Baseline	
Yes	4.27	1.23–26.94	0.019

*HEV, hepatitis E virus; OR, odds ratio; CI, confidence interval.

(March 28) in Southampton. However, 6 passengers, who were later seropositive, disembarked in New Zealand or Australia and 1 embarked in San Francisco and disembarked in Hong Kong. These dates indicate that the second leg of the cruise, from San Francisco (January 26) to Auckland (February 11), was the likely exposure period and suggest that the outbreak incubation period was 25–40 days.

A symptomatic case-patient who had late-onset disease had shared a cabin with a case-patient who had early-onset disease; the late-onset disease was potentially a secondary infection. Excluding this possible secondary case from repeat statistical analyses did not affect our results.

Information about onshore activity during this likely exposure period, including organized excursions, was available for 32 of 33 participants who had had recent acute infections. All 32 had gone ashore in Honolulu, Pago Pago, and Auckland. However, no common activities or excursions were noted, and most did not consume any food while ashore, except in Auckland. A variety of foods were consumed while ashore, and no common food was identified. Overall, analysis of excursions and food and drink consumed while ashore during the second leg of the cruise found no evidence that the infection was acquired while ashore.

Association between shellfish consumption while on board and recent HEV infection was further investigated. All seafood had been frozen; most was put on board in Southampton, but some was sent later from the United Kingdom or purchased in Australia. Lists of seafood used on board during the cruise were provided by the cruise ship company. Seafood was served on 34 of 38 days between Southampton and Sydney. Prawns and mixed seafood (mixture of shrimp or small prawns, salmon, cod, mussels, hake, and squid) were served most frequently. Implicating any particular shellfish was difficult because crab, lobster, mussels, scallops, shrimp, prawns and mixed seafood were all served at least 1 time during the suspect period of travel between San Francisco and Auckland.

Discussion

This hepatitis E outbreak among passengers during a 3-month world cruise was reported at the end of the cruise, after passengers had already disembarked and returned home. Nevertheless, the fact that approximately one third of eligible passengers were able to give blood samples within a short time enabled detection of an acute antibody response. The testing algorithm was adopted on the basis of the onset dates of the first 4 cases and the expected time delay between contacting the passengers and actually receiving samples in the laboratory for testing. It was therefore thought to be unlikely that screening for HEV RNA would provide a useful marker of recent acute infection.

One study limitation was that participants were self-selected and may not therefore represent a random sample of passengers on the cruise. Also, the time between the cruise and completion of questionnaires may have made recalling foods consumed during the cruise difficult. However, most returned questionnaires were completed comprehensively, leaving no reason to suspect differential recall between case-patients and others.

Evidence of recent acute hepatitis E infection was found for 33 participants. The evidence of past infections for 162 (21%) is consistent with hepatitis E seropositive rates of ≈25% of UK residents >55 years of age (*9*). Only 11 participants with acute infection reported illness compatible with hepatitis; 22 (two thirds) were asymptomatic or had unrelated symptoms. This investigation provided a unique opportunity to diagnose asymptomatic infection in an exposed group and found a much higher asymptomatic rate than previously reported (≈3%–4%) (*3*,*10*). Elevated liver function test results appeared to be associated with symptomatic cases; however, because those without apparent clinical signs were tested a longer time after exposure, their liver function could have returned to within reference limits.

HEV RNA was detected in only 3 case-patients, suggesting that RNA had cleared by the time most samples were tested. Virus RNA sequences were identical and belonged to genotype 3, suggesting a common-source outbreak. Genotype 3 is the main type of HEV found in industrialized counties, including the United Kingdom. Although it has also been reported in North America, Southeast Asia, Australia, and New Zealand (*4*), the genotype 3 virus found in this outbreak had close sequence homology with genotype 3 strains reported in Europe.

The evidence implicates the second leg of the cruise (January 26–February 11). Although infection could have

been acquired while ashore, the epidemiologic investigation suggests that exposure occurred while on board the ship. The estimated incubation period for this outbreak, 25–40 days, is shorter than but within the range of the reported incubation period for hepatitis E (15–60 days) (*3*).

The 3 associated risk factors (gender, age, shellfish consumption) remained significant in multivariate analysis. First, male passengers were more likely to have been infected than female passengers; 76% of recent acute infections were in men. A marked excess of indigenously acquired HEV cases in middle-age and elderly men has been reported in England, Wales (*5*), and other European countries (*10*–*12*). Our study suggests that this observed excess is not caused by ascertainment bias because men are at higher risk for disease, but rather it appears to be a genuine difference in exposure. Second, alcohol consumption was associated with recent infection. Although excess alcohol consumption could compromise hepatic function and predispose to symptomatic hepatitis E infection, as suggested by our study, alcohol consumption is probably not causally linked to exposure. The association may indicate a propensity for risk behavior that could not be controlled for in the analysis. Third, consumption of shellfish on board the ship was strongly associated with HEV infection. Further analysis did not implicate a particular type of shellfish, and cross-contamination of shellfish from a single vehicle is possible, but because the virus is waterborne and has been shown to contaminate shellfish (*13*–*15*), this association is biologically plausible. Other studies have shown that HEV can be foodborne, and illness has been linked to consumption of undercooked or raw meat (*16*–*18*).

Many of the 33 recent acute HEV infections, predominantly in men who drank alcohol, were asymptomatic and would otherwise have gone undiagnosed. We found no evidence of continuing transmission, other than 1 potential secondary case, or of any breaches of public health standards on board the ship. However, the analytical study and supporting genotype findings challenged the initial assumption that the outbreak was due to infection acquired while ashore. This investigation suggests that shellfish, which are known to be a common source of other viral infections, are a potential source of HEV infection in Europe.

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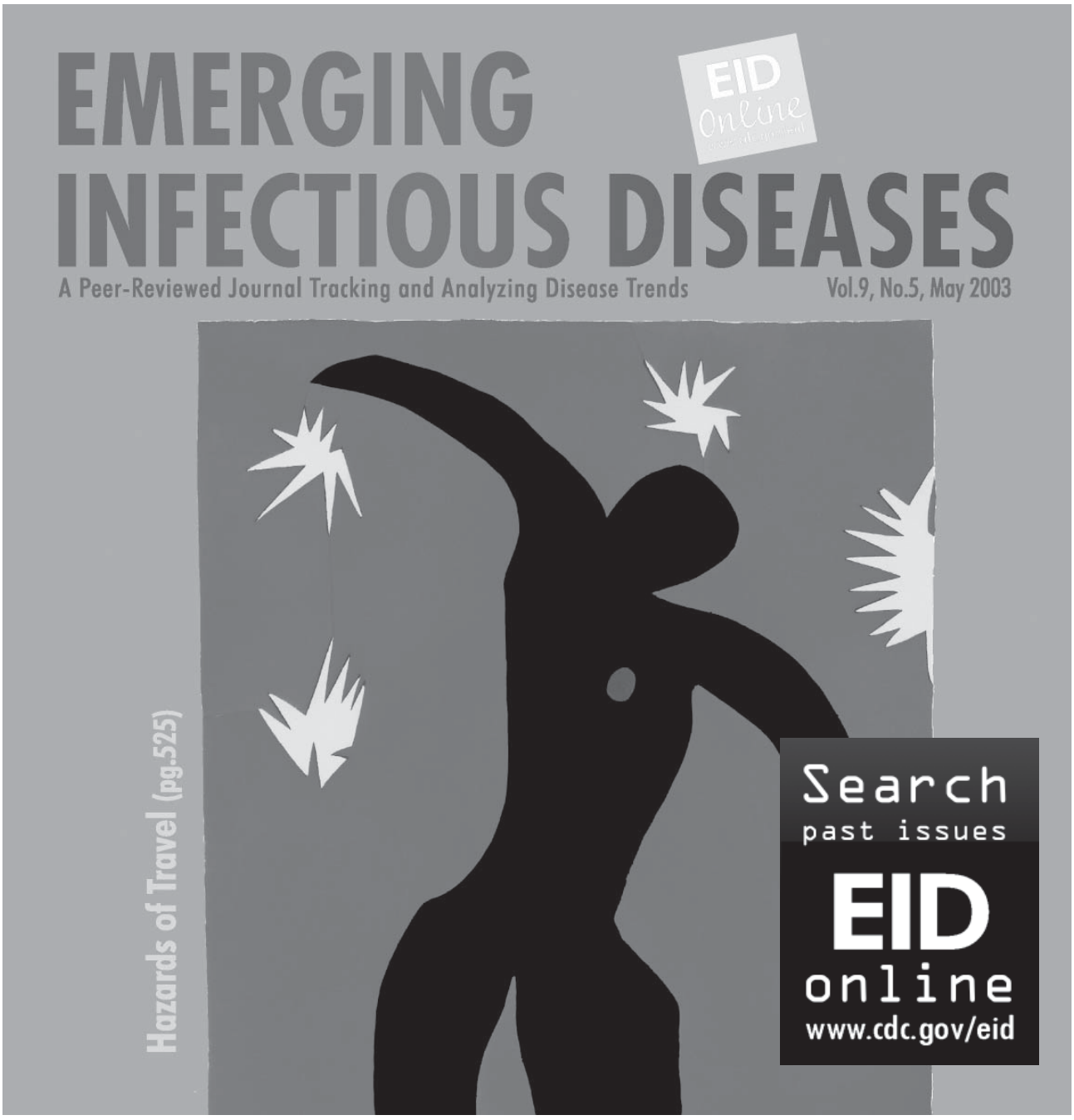

Imported Infectious Diseases in Mobile Populations, Spain

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Migration has contributed to the emergence of certain infectious diseases. To determine which infectious diseases were most common among 2 mobile immigrant groups (sub-Saharan Africans and Latin Americans) in Spain, we analyzed health and demographic characteristics of 2,198 immigrants referred to the Tropical Medicine Unit of Ramón y Cajal Hospital over a 20-year period. The most frequent diagnoses were for latent tuberculosis (716 patients [32.6%]), filariasis (421 [19.2%]), hepatropic virus chronic infection (262 [19.2%]), intestinal parasites (242 [11.0%]), and malaria (212 [9.6%]). Health screening of immigrant populations is needed to ensure early diagnosis and treatment of potentially transmissible infections.

Migration to the European Union has increased exponentially during the past 2 decades, with 1.9 million new registered immigrants in 2008 alone (*1*). Of these, 700,000 arrived in Spain, currently the main recipient country in Europe. The number of documented immigrants in Spain increased from 0.5 million in 1995 to 5.2 million on January 1, 2008, representing 11.3% of the country's total population (*2*). Thus, Spain may be representative of the impact of migration on certain emerging infectious diseases.

In mobile populations, characteristics and time of acquisition of infections depend on exposure in the original country, during migration, and in the resettlement environment, leading to considerable heterogeneity in presentation. With a few exceptions (e.g., American trypanosomiasis), most tropical infections present no transmission risk for the host population (*3*). However, other infections that affect immigrants and are not exclusive to tropical areas, such as tuberculosis (TB) and HIV, can be transmitted (*4*). Because infections can be introduced in previously unexposed populations and incidence of preexisting infections highly prevalent in countries of origin may increase, the impact of mobile populations on public health should be addressed.

This article compares the characteristics and relevance of infectious diseases in 2 mobile immigrant groups in Spain: sub-Saharan Africans and Latin Americans. Two aims of the study were to improve awareness among clinicians of emerging infections associated with human mobility and to provide additional information about imported diseases. Appropriate medical management also would be expected to affect public health.

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Methods

Study Population

The Tropical Medicine Unit (TMU) is a referral center at the infectious diseases department of the Ramón y Cajal Hospital in Madrid, Spain. In parallel with clinical work, we collected data about Latin American and sub-Saharan African immigrants seeking health care at TMU from April 1989 through June 2008 and conducted an epidemiologic and clinical study. We excluded from the study immigrants classified as visiting friends and relatives, patients lost to follow-up, and patients with incomplete tests as of June 2008.

In Spain, basic health coverage is universal, and patients need only to possess a health card. Immigrants can acquire this card regardless of their residency status (legal or illegal). If cultural or linguistic differences make obtaining a health card difficult, immigrants can be referred by nongovernmental organizations (NGOs). Patients are therefore referred from primary caregivers, specialists, or NGOs, or they can seek medical care on their own initiative (because of symptoms or to request a health examination).

Most immigrants seen at our unit have migrated for social or economic reasons and are from outside the European Union, primarily Latin America and sub-Saharan Africa.

Diagnoses

Demographic variables included age, sex, country of origin, health coverage (defined as holding Spain's national health card), and preconsultation period (defined as months from arrival in Spain to first consultation at TMU). We grouped patients' primary reasons for seeking medical assistance at TMU into 10 syndromes: dermatologic, febrile, gastrointestinal, respiratory, genitourinary, neurologic, musculoskeletal, hematologic–anemia, hematologic–eosinophilia, and asymptomatic. Each patient could be assigned to ≥1 of these categories.

Screening for asymptomatic patients comprised blood count, biochemistry, basic urinalysis, HIV serologic analysis, hepatitis B virus (HBV) and HCV serologic analysis, rapid plasma reagin, Mantoux skin test, stool parasites, PCR for malaria in sub-Saharan Africans (since 2005), and Chagas disease serologic analysis (immunofluorescent antibody test, ELISA) and PCR (since 2003) in persons from Latin America. Infectious diseases were diagnosed following standard techniques and grouped into 4 categories.

The first category was tropical infectious diseases, which were infections typically imported from tropical areas into Spain, even though some may be distributed worldwide. Examples include filariasis, malaria, trypanosomiasis, cysticercosis, schistosomiasis, and intestinal parasites.

The second category was transmissible infectious diseases, which were infections distributed globally but more prevalent in the countries of origin, with a high risk for transmission in the host country and that comprise a substantial proportion of cases in Spain. Examples include latent and active TB, acute and chronic infections with hepatotropic virus, sexually transmitted infections (STI), HIV infection, and leprosy.

The third category was common infectious diseases, which were infections distributed worldwide and prevalent in tropical and nontropical areas but which are not the focus of this study. Examples include respiratory tract infections, gastrointestinal bacterial infections, and urinary tract infections.

The fourth category was infrequent infectious diseases, which were infections with <10 cases per diagnosis. Examples include toxoplasmosis, amebic liver abcesses, and leishmaniases.

Statistical Analysis

We calculated frequency rates for reason for referral and infectious diagnoses for Latin Americans and sub-Saharan Africans. Qualitative variables were compared using the χ^2 test, the Fisher exact test, or the χ^2 test for linear trends when necessary. For quantitative variables, the Student t test for nonpaired variables or the Mann-Whitney U test were used. Significance was designated at $p<0.05$. All tests were performed with the SPSS 15 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics of the study population are shown in Table 1. The most frequent countries of origin for sub-Saharan African immigrants were Equatorial Guinea (35.7%), Nigeria (13.3%), Senegal (7.4%), and Cameroon (6.2%); for Latin Americans, they were Ecuador (34.9%), Bolivia (27.8%), Peru (11.2%), and Colombia (8.8%).

During the 20-year study period, the number of patients seen increased significantly ($\beta = 10$, $p<0.001$), as did the proportion of men and the proportion of Latin American immigrants. Three other variables (preconsultation period, age, and health coverage) did not differ significantly. Table 2 shows frequencies for each reason for seeking medical assistance according to areas of origin and grouped in 10 syndromes.

For 2,088 (95.0%) of the 2,198 patients a final diagnosis of infectious or noninfectious diseases was made; 110 (5.3%) had no evidence of illness. Of patients who received ≥1 diagnosis. 1,377 (65.9%) had multiple diagnoses (≥10/patient): 34.1%, 28.9%, 17.8%, 10.1%, and 4.5% had 1, 2, 3, 4, and 5 diagnoses, respectively. Among those classified as asymptomatic at first consultation, 87.8% had evidence of chronic disease (e.g., hypertension, diabetes, hypercholesterolemia, iron deficiency anemia, hemoglobinopathies, thyroid disease) or various infections (Tables 2–4).

Table 1. Demographic characteristics of immigrant population seeking care at the Tropical Medicine Unit, Ramón y Cajal Hospital, Madrid, Spain, 1989–2008*

Characteristic	Total	Sub-Saharan Africans	Latin Americans	p value
Study participants, no. (%)	2,198 (100)	1,564 (71.2)	634 (28.8)	
Male sex, no. (%)	1,303 (59.3)	882 (56.4)	421(66.4)	<0.001
Median age, y (IQR)	29 (22–36)	28 (22–35)	32 (24–40)	
Median preconsultation period, mo†	7	5	19	<0.001
Health coverage,‡ no. (%)	739 (33.6)	348 (22.3)	391(61.7)	<0.001

*IQR, interquartile range (25th–75th percentile).
†Defined as months elapsed from arrival to Spain to first consultation at the Tropical Medicine Unit.
‡Defined as holding Spain's national health card.

Table 2. Immigrants' reasons for seeking medical assistance, by area of origin, Tropical Medicine Unit, Ramón y Cajal Hospital, Madrid, Spain, 1989–2008*

Syndrome	Total population, no. (%), N = 2,198	Sub-Saharan Africans, no. (%), n = 1,564	Latin Americans, no. (%), n = 634	p value
Hematologic–eosinophilia	570 (26)	435 (28)	135 (21.3)	0.002
Dermatologic	544 (24.7)	477 (30.5)	67 (10.6)	0.001
Fever	451 (20.5)	351 (22.4)	100 (15.8)	0.001
Asymptomatic	396 (18)	268 (17.1)	128 (20.2)	0.09
Gastrointestinal	363 (16.5)	269 (17.2)	94 (14.8)	0.608
Respiratory	314 (14.3)	209 (13.4)	105 (16.6)	0.006
Hematologic–anemia	283 (12.9)	230 (14.7)	53 (8.4)	0.001
Genitourinary	234 (10.6)	198 (12.7)	36 (5.7)	0.001
Neurologic	219 (10)	144 (9.2)	75 (11.8)	0.03
Musculoskeletal	169 (7.7)	141 (9)	28 (4.4)	0.001

*Because each patient could have ≥1 main reason for seeking medical assistance, the number of cases can be higher than the number of patients. Percentages were calculated as number of cases divided by number of patients in each group (total population, sub-Sahara African immigrants, or Latin American immigrants).

Tropical Infectious Diseases

Filariasis

We found 421 filariasis cases, of which most occurred in sub-Saharan Africans. Of these, 258 were *Onchocerca volvulus* infections, 124 were *Mansonella perstans* infections, 29 were *Loa loa* infections, and 7 were *M. streptocerca* infections. Three cases in Latin American patients were caused by *O. volvulus* infections.

Intestinal Parasites

Intestinal parasites were diagnosed in 242 patients, mostly from sub-Saharan Africa. The most frequent parasites identified were *Ascaris lumbricoides* (35.5%) and *Giardia intestinalis* (28.5%).

Malaria

Malaria, diagnosed in 212 patients, occurred significantly more often in sub-Saharan Africans than in Latin Americans. The median preconsultation period was 2 months. Fifteen (7.1%) patients were asymptomatic when their malaria was diagnosed. Among the 199 sub-Saharan African malaria patients, 125 were infected with *Plasmodium falciparum*, 13 with *P. malariae*, 10 with *P. ovale*, 4 with *P. vivax*, 8 with mixed infections (5 with *P. falciparum* and *P. malariae*, 2 with *P. falciparum* and *P. ovale*, and 1 with *P. malariae* and *P. ovale*), and 39 with *Plasmodium* sp. where specific species could not be determined, generally because the diagnosis was made when PCR was not available. Malaria was diagnosed in 13 Latin American patients; 10 had *P. vivax* infections and 3 had *P. falciparum* infections.

Chagas Disease

Of the 101 cases of Chagas disease diagnosed, all were in Latin American patients, with 95.0% from Bolivia, and most cases (71.3%) occurred in men. Of Chagas disease cases, 42.6% were asymptomatic and were detected after routine screening. Organ involvement was found in 20.7% of patients; 17.5% had cardiac disease, 2.0% had gastrointestinal involvement, and 1.2% had both.

Transmissible Infectious Diseases

Tuberculosis

Latent TB infection (716 cases) occurred significantly more often in sub-Saharan African than Latin American patients. Active TB (107 cases) occurred more often among Latin Americans; the highest proportions of patients were from Ecuador (21.4%) and Peru (17.5%). The median preconsultation period was 12 months. Of active TB cases, 75 (70.1%) were pulmonary TB and 32 (30%) were extrapulmonary TB. Co-infection with HIV and active TB was detected in 12 (11.2%) patients, mostly from sub-Saharan Africa (75.0%).

Hepatitis

A total of 262 patients had chronic infection with hepatitis viruses. The prevalence was higher in sub-Saharan Africans. The most frequently identified chronic hepatitis virus was HBV (60.7%). The prevalence of hepatitis B surface antigen in sub-Saharan African patients was 9.8%. The prevalence of coinfection with HBV and HCV was 1.6%, and 0.9% with HBV and hepatitis D virus. Acute hepatitis infection was diagnosed infrequently: 41 (1.4%) cases, with no significant differences between the 2 groups. In addition, 797 patients had evidence of past HBV infection, of whom 277 (34.7%) had antibody to virus core or virus core protein; 95.7% were from sub-Saharan Africa.

Sexually Transmitted Infections and HIV

STIs were found in 112 patients, mainly from sub-Saharan Africa. Sixty-seven patients had latent syphilis, 17 had bacterial vaginosis, 12 had trichomoniasis, 9 had genital herpes, 4 had *Chlamydia trachomatis* infections, and 3 had gonococcal urethritis. Among patients in whom

Table 3. Disease diagnoses in immigrants, by area of origin, Tropical Medicine Unit, Ramón y Cajal Hospital, Madrid, Spain, 1989–2008*

Diagnostic category and disease	Total population, no. (%), N = 2,198	Sub-Saharan Africans, no. (%), n = 1,564	Latin Americans, no. (%), n = 634	p value
Tropical infectious diseases				
Filariasis	421 (19.2)	418 (26.7)	3 (0.4)	0.001
Intestinal parasites	242 (11.0)	162 (10.4)	80 (12.6)	0.15
Malaria	212 (9.6)	199 (12.7)	13 (2.1)	0.001
Chagas disease	101 (4.5)	0	101 (15.9)	
Schistosomiasis	39 (1.8)	38 (2.4)	1 (0.2)	0.001
Cysticercosis	31 (1.4)	3 (0.2)	28 (4.4)	0.001
Transmissible infectious diseases				
Latent tuberculosis	716 (32.6)	596 (61.2)	120 (18.9)	0.001
Active tuberculosis	107 (4.8)	52 (3.3)	55 (8.7)	0.001
Hepatotropic virus, acute infection†	31 (1.4)	27 (1.7)	4 (0.6)	0.075
Hepatotropic virus, chronic infection‡	262 (11.9)	257 (16.4)	10 (1.6)	0.001
Sexually transmitted infections§	107 (4.9)	92 (5.9)	15 (2.4)	0.002
HIV infection	97 (4.4)	82 (5.2)	15 (2.4)	0.005
Leprosy	8 (0.4)	3 (0.2)	5 (0.8)	0.02
Common infectious diseases				
Respiratory infections	61 (2.8)	36 (2.3)	25 (3.9)	0.013
Gastrointestinal bacterial infections	92 (4.2)	69 (4.4)	23 (3.6)	0.705
Urinary infections	69 (3.1)	45 (2.9)	24 (3.8)	0.135
Skin infections	80 (3.6)	71 (4.5)	9 (1.4)	0.001
Infrequent infections	36 (1.7)	20 (1.3)	16 (2.5)	0.025
Noninfectious diseases	596 (27.1)	430 (27.5)	166 (26.2)	0.978

*Because each patient could have >1 diagnosis, the number of cases can be higher than the number of patients. Percentages have been calculated as number of cases divided by number of patients in each group (total population, sub-Sahara African immigrants, or, Latin American immigrants).
†Acute infections with hepatotropic virus caused by hepatitis A virus, hepatitis B virus, hepatitis E virus, cytomegalovirus, and Epstein-Barr virus
‡Chronic infections with hepatotropic virus were caused by hepatitis B virus, hepatitis C virus, and hepatitis D virus.
§Sexually transmitted infections comprised syphilis, bacterial vaginosis, trichomoniasis, gonococcal urethritis, *Chlamydia trachomatis*, and genital herpes virus.

syphilis was diagnosed, 59 (88.0%) were from sub-Saharan Africa and 8 (11.9%) were from Latin America, 36 (53.7%) were men, and 10 (15%) were co-infected with HIV. Six were asymptomatic when they sought care at TMU. HIV was diagnosed in 97 patients; 19 were asymptomatic and 82 (84.5%) were from sub-Saharan Africa.

Infrequent Infections

Nine patients had toxoplasmosis, 8 had amebic liver abscesses; 5 had rickettsiosis; 4 had *Fasciola hepatica* infections; 2 each had cutaneous leishmaniasis, mucocutaneous leishmaniasis, and brucellosis; and 1 each had visceral leishmaniasis, hydatid disease, borreliosis, and human T-lymphotrophic virus type 1 infection. These infrequent infections occurred proportionally more frequently among Latin American than among sub-Saharan African patients.

Discussion

The large size of the population analyzed and the long time period (≈20 years) add strength to the study. Because one third of the study population were considered illegal aliens and lacked health insurance, our analysis was able to provide valuable information about infections affecting a group that is frequently not adequately represented in published studies because of the usual restrictions on access to health services. Nonetheless, this study is subject to several limitations.

In Spain, most immigrants come from a European Union member state (Romania, 14% of all immigrants in Spain), followed by northern Africa (Morocco, 12%) and Latin America (Ecuador, 8%) (*2*). Extrapolation of the results of this study to the global immigrant population may therefore be limited. However, these mobile groups are important because of the spectrum of imported diseases represented. This applies both to tropical diseases and transmissible infections (*5*).

Comparison based on geographic distribution may exclude other important aspects involved in the development of certain infectious diseases: socioeconomic status of the country, public health infrastructure, rural or urban origin, or reason for migration. However, characteristics of most immigrants seen at TMU were similar: most came from tropical, underdeveloped areas of Latin America and sub-Saharan Africa, and most migrated for economic reasons.

During the 20 years of data collection, diagnostic methods and screening procedures changed, thus influencing results over time. Depending on how the patients were referred to our clinic the frequency of the various diseases reported cannot be interpreted as prevalence rates in the 2

Table 4. Infectious diseases diagnoses in asymptomatic patients, Tropical Medicine Unit, Ramón y Cajal Hospital, Madrid, Spain, 1989–2008

Diagnostic category and disease	Asymptomatic cases, no. (%), n = 396
Tropical infectious diseases	
Filariasis	36 (9.1)
Intestinal parasites	35 (8.8)
Malaria	15 (3.8)
Chagas disease	43 (10.9)
Schistosomiasis	5 (1.3)
Cysticercosis	0
Transmissible infectious diseases	
Latent tuberculosis	160 (40.4)
Active tuberculosis	3 (0.7)
Hepatotropic virus, acute infection*	2 (0.5)
Hepatotropic virus, chronic infection†	40 (10.1)
Sexually transmitted infections‡	10 (2.5)
HIV infection	19 (4.8)
Leprosy	0
Common infectious diseases	
Respiratory tract infections	0
Gastrointestinal bacterial infections	10 (2.5)
Urinary tract infections	9 (2.3)
Skin infections	9 (2.3)
Infrequent infections	8 (2.0)

*Acute infections with hepatotropic virus caused by hepatitis A virus, hepatitis B virus, hepatitis E virus, cytomegalovirus, and Epstein-Barr virus.
†Chronic infections with hepatotropic virus were caused by hepatitis B virus, hepatitis C virus, and hepatitis D virus.
‡Sexually transmitted infections comprised syphilis, bacterial vaginosis, trichomoniasis, gonococcal urethritis, *Chlamydia trachomatis*, and genital herpes virus.

migrant populations considered. Because most individuals were referred for investigation of symptoms or diseases, the frequency observed can be expected to be higher than in the overall migrant population.

Demographic variables of age and sex are in accordance with national data on immigrant populations (*2*) and are similar to other series (*6*,*7*), except for the larger proportion of males in the Latin American group. The significant difference in the preconsultation periods of the 2 groups might be explained by the larger proportion of Latin Americans who held health cards and thus were seen initially by general practitioners. Because most sub-Saharan African immigrants were undocumented and referred from NGOs, TMU was their first contact with the public health system. Nevertheless, the proportion of Latin Americans seen at TMU as a result of active health promotion campaigns and screening for Chagas disease increased.

Consistent with other series (*8*), the most frequent reasons for seeking medical assistance at TMU were hematologic–eosinophilia, dermatologic syndrome, and fever. All syndromes occurred significantly more often in sub-Saharan Africans, except for respiratory and neurologic. Geographic variation in disease distribution would explain certain differences. The increased frequency of dermatologic syndrome and eosinophilia in Africans could be due to the greater incidence of filariasis; anemia could result from nutritional deficiencies and hemoglobinopathies; and fever could be due to malaria. For Latin Americans, increased prevalence of neurocysticercosis and TB might explain the increased frequency of neurologic and respiratory syndromes.

The most common tropical disease was filariasis, with onchocerciasis the most frequent filarial infection, affecting sub-Saharans significantly more often than Latin Americans. More than 99% of symptomatic onchocerciasis occurs in western sub-Saharan Africa, where most of the patients in the study originated. The number of cases diagnosed at TMU, however, has progressively decreased since 2000. Screening for filariasis by microfilaremia detection and skin snips should probably be considered in patients presenting pruritus or eosinophilia (*9*).

In Europe, as in Spain, immigrants account for approximately 50% of malaria cases (*10*). In our series, as in other national (*11*) and international (*12*) studies, most malaria patients were from sub-Saharan Africa, and the most commonly isolated species was *P. falciparum*. However, *P. vivax* was the principal species diagnosed in Latin Americans. A considerable number of patients were asymptomatic at diagnosis, probably because of partial immunity developed during residence in areas to which malaria is endemic (*13*) and the implementation of PCR for *Plasmodium* spp. as a screening test in sub-Saharan Africans, which enables detection of very low parasitemia. Malaria screening should be considered in newly arrived immigrants from areas to which it is endemic, regardless of clinical presentation (*14*,*15*); in specialized referral centers, such as TMU, PCR with its higher sensitivity and specificity should be available.

Migration is changing the geographic distribution of Chagas disease, which until recently has been limited to Latin America. During the 1970s, the United States was the leading recipient of Latin American migrants but Europe (especially Spain) is now a main recipient (*16*). A recent study in Spain estimated the number of immigrants potentially infected with *Trypanosoma cruzi* could range from 37,000 to 122,000 (*17*). Alternate, nonvectorial, routes of transmission (vertical or through blood transfusion or organ transplantation) and reactivation episodes in inmunosuppressed persons make Chagas disease an emerging and potentially transmissible disease in the autochthonous population, and thus an important public health concern (*18*). Furthermore, severe cardiac disease could develop in infected persons; a broader knowledge of this aspect of the disease by clinicians is necessary. In our series, prevalence reached nearly 16% among Latin Americans. Bolivian patients accounted for 95% of cases, reflecting its high endemicity (*19*). Electrocardiographic and echocardiographic

disorders were found in 15.9% and 7.3% of patients, respectively. These results suggest that all immigrants from areas to which it is endemic should be screened.

In the literature, the prevalence of intestinal parasites in immigrants ranges from 11% to 67%, depending on the origin and type of immigrant, with higher frequencies in recently arrived refugees and sub-Saharan Africans (*7*,*20*,*21*). However, we found a low prevalence (11%). The impact of intestinal parasitism is low because a considerable proportion of affected persons are asymptomatic, and illness is generally low, with certain parasites (e.g., *Strongyloides stercoralis*) (*22*). In our study, 11.5% of patients had no symptoms. These findings question the usefulness of screening the migrant population from areas to which it is endemic for intestinal parasitism. Some authors propose empiric treatment with albendazole (*23*), effective against *S. stercoralis* and *G. intestinalis* (24), as the most cost-effective measure. Others argue against this measure for reasons such as potential side effects, possible incorrect treatment of certain pathogens (e.g., *Entamoeba histolytica*), and the inherent risks of treating a patient with neurocysticercosis. Although further studies are necessary to assess advantages and risks of empiric treatment over screening (*15*) as a public health measure, an alternative approach could be selective screening of high-risk groups, such as pregnant women, children, and inmunosuppressed patients.

TB is an example of an infectious disease that has emerged with the increase in mobile populations (*25*). Prevalence of active TB among immigrants is higher than in the host population. We found active TB more often in Latin Americans than in sub-Saharan Africans, similar to other national studies (*26*). That TB prevalence rates/100,000 population are as high as 195 and 266 in Ecuador and Bolivia, respectively (World Health Organization data, 2006, http://apps.who.int/globalatlas/dataQuery/default.asp), the most common countries of origin of our Latin American group, might explain this result. Median interval from arrival in Spain to presentation with TB was 2 years, which is consistent with previous studies showing a higher risk for TB during the first 2–5 years of residence in the host country and where activation of latent TB infection seems to be a common cause of TB among immigrants (*27*). The rate of latent TB (32.6%) in our study was consistent with other series (*7*). Latent TB occurred more often in sub-Saharan Africans than in Latin Americans.

Public heath interventions for control of TB in the immigrant population are intensely debated. Many authors consider that interrupting the ongoing community TB transmission through detection and treatment of active TB and contact investigation is the best cost-effective strategy (*28*). However, current guidelines in certain countries recommend screening for latent TB in immigrants, especially those who entered the host country within the previous 5 years (*29*,*30*). Screening policies for latent TB face several difficulties, and no consensus has been reached, the best screening method is under discussion (chest radiographs, intradermal tuberculin test [IDT]), IDT interpretation is ambiguous (3 cutoff points may be considered), the false-positive rate is high because of BCG (*Mycobacterium bovis* BCG) vaccination, and ensuring high rates of treatment completion for latent TB in the migrant population has proven difficult (*31*). Nevertheless, with the implementation of new screening techniques (interferon gamma release assay) that are less affected by BCG vaccination (*32*) and use of culturally adapted programs to improve adherence to treatment, screening for latent TB followed by appropriate treatment could be a successful strategy for global TB control in Western countries. Some studies support a better, cost-effective approach to TB using screening (*33*).

Chronic HBV infection is a major health problem in sub-Saharan Africa and Asia, where prevalence is >8% (*34*). The mortality rate from chronic infection is ≈25% because of complications (liver cirrhosis and hepatocellular carcinoma). The 9.8% prevalence in our study was similar to others (*7*,*35*). In developing countries, many infections are acquired during the perinatal period, and patients develop long-term complications in early adulthood, whereas in developed countries, infection and complications occur later in life. Screening for HBV in sub-Sahara African immigrants would help detect chronic infections in young adults, allowing early treatment and monitoring for complications. This could also prompt contact screening, vaccination, and education as preventive measures (*15*). Finally, when an isolated core antibody pattern is detected, a relatively common serologic result in the sub-Saharan African population, PCR assessment for occult chronic infection for HBV DNA may be required, especially in HIV-positive patients (*35*).

STIs other than HIV and viral hepatitis were diagnosed in 4.8% of the total population studied. Most STIs were due to latent syphilis (60%), particularly in the Africans. This trend toward more bacterial STIs in certain groups, such as immigrants, is consistent with observations throughout Spain and Europe (*36*). Most STIs, particularly syphilis, can be easily misdiagnosed because they can run a mild or asymptomatic course, but complications and sequelae can be severe. Moreover, syphilis can be easily transmitted from mother to child. Intervention programs for immigrants, particularly sub-Saharan Africans, with active screening and treatment for syphilis could reduce the prevalence and transmission of this infection in the community.

In December 2007, the Joint United Nations Programme on HIV/AIDS (*37*) stated an estimated 33.2 million persons were living with HIV infection worldwide, with most (22.5 million) living in sub-Saharan Africa. In our series, HIV infection also occurred significantly more often among sub-Saharan Africans than among Latin Americans.

Throughout western Europe, HIV infection increasingly, and disproportionately, affects immigrants from countries in which the prevalence of HIV/AIDS is high and, in most countries, accounts for the majority of heterosexually acquired HIV infections diagnosed in recent years (*38*). In some series, HIV is diagnosed in immigrants and refugees at a later stage of infection, with lower CD4 cell counts, a larger proportion of females, and with different HIV subtypes (*39*). This highlights the need for screening immigrants, particularly sub-Saharans, for HIV to enable early diagnosis and treatment as well as prevention and education. A larger social and cultural program support is necessary to ensure adequate treatment as well as access to the health care system.

Increased population mobility has led to the disappearance of existing barriers for the spread of certain diseases. Characteristics of mobile populations are becoming increasingly heterogeneous (*4*). Epidemiologic studies in mobile groups help determine factors possibly associated with greater risk for certain pathologies and identify which of the latter may influence health to a greater extent. Our study may improve knowledge about pathology in 2 important mobile populations in Spain, enabling early diagnosis and treatment of potentially transmissible infections (TB), education and prevention programs (STIs, HIV) and catching up on vaccination (*40*), with ensuing positive public health repercussions. Future research may focus on development of diagnostic protocols for imported diseases on the basis of epidemiologic findings.

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Epidemic of *Plasmodium falciparum* Malaria Involving Substandard Antimalarial Drugs, Pakistan, 2003

Toby Leslie, Harparkash Kaur, Nasir Mohammed, Kate Kolaczinski, Rosalynn L. Ord, and Mark Rowland

Because of instability in eastern Afghanistan, new refugees crossed into the federally administered tribal areas of northwestern Pakistan in 2002. In 2003, we investigated an epidemic of *Plasmodium falciparum* malaria in 1 of the camps. Incidence was 100.4 cases/1,000 person-years; in other nearby camps it was only 2.1/1,000 person-years. Anopheline mosquitoes were found despite an earlier spray campaign. Documented clinical failures at the basic health unit prompted a drug resistance survey of locally manufactured sulfadoxine-pyrimethamine used for routine treatment. The in vivo failure rate was 28.5%. PCR analysis of the *P. falciparum* dihydrofolate reductase and dihyropteroate synthase genes showed no mutations associated with clinical failure. However, chemical analysis of the drug showed that it was substandard. As global incidence decreases and epidemics become more of a threat, enhanced quality assurance of control interventions is essential.

Epidemics make a major contribution to the global impact of malaria (*1*). Predisposing factors include level of disease endemicity, immune status of the population, changes in vector–person contact, unusual weather phenomena, conflict or mass population movement, and the capacity of public health systems to detect epidemics and respond (*1*). Epidemic malaria is more common in areas of mesoendemicity or hypoendemicity (*2*,*3*).

Detection and control require rapid reporting of reliable surveillance data and the capacity to analyze and interpret trends. An epidemic can be defined as a "sharp increase in the frequency of malaria transmission that exceeds by far the inter-seasonal variation normally experienced" (*4*). Distinguishing a seasonal increase from an epidemic may require comparison with historic data from the same locality (*1*,*5*), but such data may be unavailable or unreliable. This finding is particularly true for regions where conflict leads to population upheaval, creation of new settlements, and breakdown of health services (*6*,*7*). Adequate control requires rapid response using health information campaigns, reinforced diagnostic services, effective short-course drugs, preventative measures, and political commitment.

The Federally Administered Tribal Areas (FATA) of northwestern Pakistan are semiautonomous, tribally governed agencies running north–south along the western border with Afghanistan. These are areas of rugged terrain along a porous and unstable border (the Durrand Line). The region has been an area of complex emergency since 1979 and is currently unstable because of conflict between Pakistan's armed forces and insurgents in FATA and the ongoing conflict across the Durrand Line in Afghanistan.

We describe an epidemic of *Plasmodium falciparum* malaria among Afghan refugees who in 2002 had fled to FATA after drought and war in the neighboring Afghan provinces of Nangahar, Paktia, and Khost. We report the causes and epidemiology of the outbreak and the health service response.

Materials and Methods

Study Area and Health Services

For 3 decades, FATA has hosted one of the largest refugee migrations, beginning with >3 million Afghans crossing the border to escape the conflict in Afghanistan (*8*). In response to the initial refugee crisis, >200 refugee camps were established under the mandate of the United Nations High Commissioner for Refugees (UNHCR) and

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the Pakistan Commissionerate for Afghan Refugees. Primary healthcare was provided by nongovernmental organizations through basic health units (BHUs) in each camp.

Ashgaroo camp was formed in 2002 in Khurram Agency, near the town of Parachinar, after drought and conflict in the neighboring Afghan provinces of Nangahar, Paktia, and Khost forced several thousand refugees to cross the border. Refugees were provided with tarpaulins and used locally acquired mud and straw to construct rudimentary shelters. The camp was situated in an area of semiarid grassland. A few kilometers to the east, the land is irrigated by the Khurram River, a tributary of the Indus River. Rice, wheat, and maize are grown in this region by the local Pakistani population. The UNHCR demographic surveillance system showed that the population of the camp varied between 8,000 and 10,000 (HealthNet TPO, 2005, unpub. data).

Malaria is seasonal in the region; ≈85% of cases are caused by *P. vivax* and the remainder by *P. falciparum* (*6*). An integrated malaria control program was run through the UNHCR network of clinics and field laboratories; technical support was provided by the nongovernmental organization HealthNet TPO. First-line treatments were sulfadoxine-pyrimethamine (SP) for patients with *P. falciparum* malaria and chloroquine for patients with *P. vivax* malaria.

Analysis of Malaria Surveillance Data

Routine malaria surveillance data were the primary data source for analysis of the epidemic. These data were compiled each month by BHU staff in each refugee camp and transmitted through the health information system to provincial health authorities. Health services were free and most refugees used the BHUs. Outpatients with suspected malaria were referred to a microscopist for diagnosis. Patients with confirmed malaria were treated according to local guidelines with chloroquine for *P. vivax* and SP for *P. falciparum* or mixed infections. The quality assurance system, using blinded cross-checking of positive and negative slides, ensured a field microscopy accuracy >98% (*9*).

Case records entered in malaria registers consisted of age, sex, slide result, and treatment given. The total number of slides examined and the age and sex of persons with *P. vivax*, *P. falciparum*, and mixed infections were submitted each month to HealthNet TPO and collated by camp into monthly summaries of numbers of malaria cases, slide positivity rate, and incidence.

To compare with Ashgaroo data, 2 other datasets were accessed from the surveillance data of the Kurram Agency for 2002–2004. The first dataset was summary data for the camps of Bassoo and Old Bagzai which were established for new refugees at the same time as Ashgaroo. The second dataset was summary data for 6 camps established in Kurram in the early 1980s; these camps have longer established health services. All camps were similar in that they were occupied by Afghan refugees and situated in the same locality (Khurram Agency). The older camps had mud houses and a well-established health system. Newer camps were a mixture of tarpaulin shelters with mud walls, were more remotely situated, lacked electricity, and had a recently established health center.

Analysis of the epidemic compared 3 parameters: number of cases of malaria in persons who came to BHUs, slide positivity rate (no. cases positive for malaria/total no. slides examined), and incidence rate (no. cases/total person-months at risk). These parameters were estimated by using population data from UNHCR and passive surveillance data from camp BHUs.

Monitoring of Drug Resistance

Monitoring of drug resistance was conducted in response to reports of treatment failure. Patients with microscopically confirmed *P. falciparum* infection gave informed consent and were enrolled in an in vivo drug resistance study. These patients were administered the same locally manufactured SP used by BHU health workers for routine treatment. The dose administered was based on weight of the patient and was noted on patient record forms. Patients were monitored for vomiting. Patients returned for consultation and collection of blood smears at weekly intervals for 42 days or at any time if symptoms recurred. Any absentee was followed up in their shelters and classified as lost to follow-up if absent for >2 consecutive days. Treatment failures in patients were defined by using criteria of the World Health Organization (WHO) (*10*); these patients were treated with mefloquine. A blood sample was obtained at the time of enrollment for detection of mutations in the *P. falciparum* dihydrofolate reductase (*Pfdhfr*) and dihyropteroate synthase (*Pfdhps*) genes, which are known to be associated with antifolate resistance (*11*,*12*).

An in vivo resistance study was conducted concurrently by HealthNet TPO in 3 long-established refugee camps 50–100 km north of the study site and situated outside the tribal areas. As in Ashgaroo, patients were enrolled if they had microscopically confirmed *P. falciparum* malaria but these patients were treated with SP (500 mg sulfadoxine and 25 mg pyrimethamine) (Fansidar; Roche, Basel, Switzerland) provided by WHO. Supervision was the same as in Ashgaroo, with a 42-day observation period. Slides from both trials were read by 2 microscopists and discordant slides were read by a third. In both studies, the primary outcome was defined as any malaria treatment failure, whether clinical or parasitologic, over the 42-day observation period. Simple proportions and univariate and multivariate logistic regression analyses were used to assess associations with failure, correcting for sex and age (STATA version 8; StataCorp., College Station, TX, USA).

Drug Quality Evaluation

SP (Fansidar; Roche) and the locally manufactured SP were analyzed for quantity of active ingredient by using in vitro dissolution testing protocols according to procedures outlined in the United States Pharmacopeia and by high-performance liquid chromatography (HPLC). The test for content expresses the amount of active ingredient as a percentage of the label claim, and the test for dissolution determines the amount of active ingredient released and available for absorption (*13*).

Tablet dissolution was performed in the Pharma Test PT 017 dissolution apparatus (Pharma Test Apparatebau, Hainburg, Germany) and analyzed by using HPLC (*14*). Drug quality was assessed by comparing the amount of active ingredient in eluents of each dissolution sample against a known concentration of the standard for sulfadoxine and pyrimethamine after HPLC analysis.

Vector Control

Entomologic investigation was conducted by space spray collection of mosquitoes conducted in 5 randomly selected compounds (animal sheds and sleeping areas) in Ashgaroo camp on 1 day. Windows were sealed and rooms were sprayed with a pyrethroid spray canister. Specimens were collected from white floor sheets and identified to species.

Results

Initial Outbreak Investigation and Response

In late June 2003, cases of *P. falciparum* malaria were reported in Ashgaroo camp. Because cases are not usually seen before mid-August, an investigation was mounted that strengthened case reporting and treatment guidelines. By August, the number of cases in Ashgaroo had increased above the usual level for the time of year. The epidemic response team directed to the camp confirmed a high vector density. A total of 717 anopheline specimens were collected from the 5 compounds, mostly from animal sheds. Of these specimens, 690 (96%) were *Anopheles subpictus*, 6 were *A. stephensi*, 14 were *A. culicifacies*, and data for 7 were not available. Anopheline larvae were found in several locations, mainly in borrow pits recently dug by the refugees for construction of mud shelters. Typically, borrow pits were several meters wide and deep and fed by water drained from the camps' water tanks or from unseasonable rain, which maintained adequate water levels for mosquito breeding.

The epidemic response was to ensure adequate supplies of drugs, provide diagnostic and treatment services 24 hours per day, and apply larvicide to confirmed breeding sites. Insecticide-treated nets were made available at a highly subsidized price (UNHCR policy at the time). Active case detection was not carried out until October and November.

Epidemic Trends

Malaria Cases

The trend in number of malaria cases recorded during 2002–2004 is shown in Figure 1. A steep increase in the number of *P. vivax* cases in the 3 new camps of Ashgaroo, Bassoo and Old Bagzai began in June 2002 at the beginning of the transmission season and peaked in August 2002 (Figure 1). In 2003, the increase in cases started much earlier, a normal occurrence because of delayed patency or relapse of cases from the previous year's transmission. Insecticide spraying of Bassoo and Old Baghzai in 2003 appeared to reduce the number of *P. vivax* and *P. falciparum* cases that otherwise occurred that summer by curtailing transmission.

The *P. falciparum* malaria epidemic in Ashgaroo developed rapidly from 17 cases in August 2003 to 438 in September 2003. By November, the number of cases (82) had decreased to levels expected for that time of year. Using routinely reported mortality data as the indicator, we did not observe excess deaths in the camp. Few co-infections were recorded (1 in 2002 and 22 in 2003).

Malaria Incidence

An unusually high incidence of *P. vivax* malaria was recorded in the 3 newly established refugee camps (Ash-

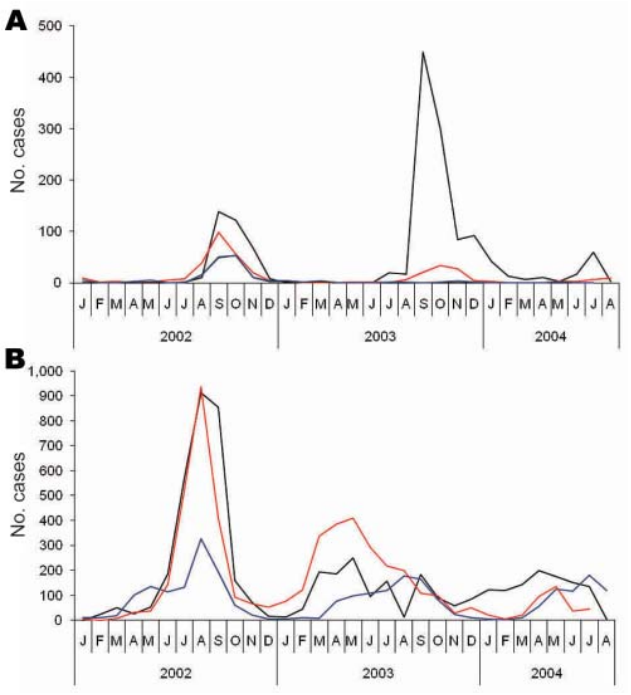

Figure 1. Number of cases of A) *Plasmodium falciparum* and B) *P. vivax* malaria in refugee camps in Khurram Agency, Pakistan, 2002–2004. Black lines indicate Ashgaroo camp, red lines indicate Bassoo and Old Bagzai camps combined, and blue lines indicate the remaining 6 older camps.

garoo, Old Bagzai, and Bassoo) in the summer of 2002 (Table 1, Figure 2). Incidence of *P. vivax* (269 cases/1,000 person-years) and *P. falciparum* malaria (32 cases/1,000 person-years) was 15.6× higher (95% confidence interval [CI] 14.7–16.7×] for *P. vivax* and 6.9× higher (95% CI 5.9–8.1×) for *P. falciparum* than in the 6 remaining camps. The range in annual incidence of *P. vivax* malaria in the 3 new camps was similar (130–296 cases/1,000 person-years). In contrast, the annual incidence of *P. falciparum* malaria was similar in Ashgaroo (32 cases/1,000 person-years) and Bassoo (22 cases/1,000 person-years) but was ≈10× lower than the annual incidence of *P. vivax* malaria (269 cases/1,000 person-years).

Tents and houses were sprayed with insecticide before the onset of the 2003 malaria transmission season. During 2003, a total of 963 *P. falciparum* malaria cases were recorded in Ashgaroo (incidence 100.4/1,000 person-years). The incidence rate ratio relative to the previous year was 3.1 (95% CI 2.8–3.5). Compared with rate ratios for camps at Bassoo and Old Bagzai, the incidence rate ratio in Ashgaroo was 48.8 (95% CI 30.3–84.1). Compared with rate ratios for the 6 long-established camps, the ratio was 72.1 (95% CI 58.5–89.7). The incidence of *P. falciparum* malaria in Ashgaroo was only marginally lower than that for *P. vivax* malaria (*P. falciparum* 100.4/1,000 person-years vs *P. vivax* 142.6/1,000 person-years), whereas the *P. vivax* malaria:*P. falciparum* malaria incidence rate ratio for the region is usually of the order of 5:1.

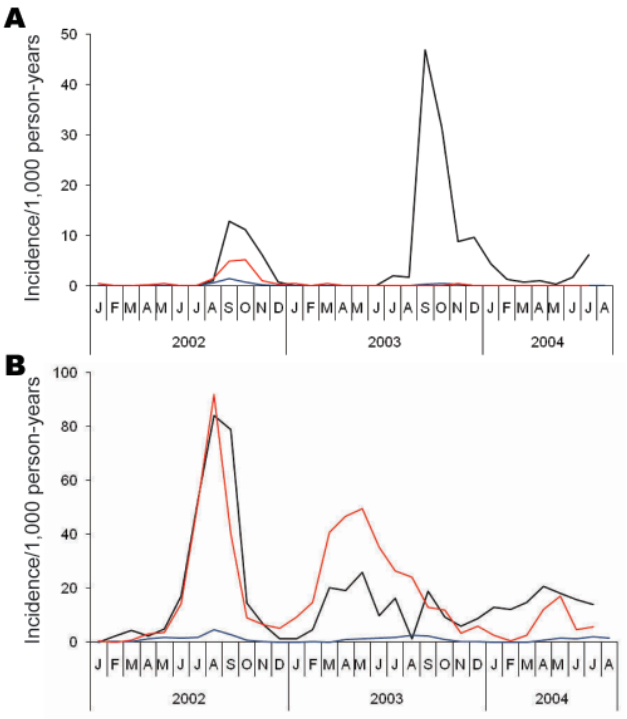

Figure 2. Incidence per 1,000 person-months of A) *Plasmodium falciparum* and B) *P. vivax* malaria in refugee camps in Khurram Agency, Pakistan, 2002–2004. Black lines indicate Ashgaroo camp, red lines indicate Bassoo and Old Bagzai camps combined, and blue lines indicate the remaining 6 older camps.

Slide Positivity Rate

The slide positivity rate provides an opportunity to measure the proportion of febrile illness attributable to malaria. The advantage of this rate over estimates of incidence rate is that trends are unaffected by inaccuracies or changes in population. During epidemics, malaria positivity rates show a sudden increase. *P. viv*ax positivity rates for the new camps in 2002 and 2003 were only 2.9× higher than for long-established camps (Figure 3), and *P. falciparum* positivity rates for the new camps of Ashgaroo (4.7%) and Bassoo (3.6%) in 2002 were also similar to those for the older camps (2.9%). However, in 2003, the *P. falc*iparum positivity rate showed a marked increase for Ashgaroo (18.8%) and reached 50% positivity during the peak of the epidemic in October, a rate 9× higher than for the neighboring camps.

Evaluation of Drug Efficacy

In September 2003, staff reported that many patients were returning with recurrent malaria after treatment with SP. These cases were confirmed microscopically and treated with mefloquine, the second-line treatment. Using the in vivo drug resistance protocol, we recruited 169 patients with malaria cases at the clinic and who were treated with SP (Table 2). Selection was based on clinical symptoms, malaria parasitemia, and granting of informed consent. Eighteen (10.6%) patients were lost to follow-up. Of those completing the study, treatment was not successful in 43 (28.5%) of 151 patients (Table 3). The comparison group showed a failure rate for treatment with SP from WHO of only 10% (4/40) ($\chi^2 = 5.8$, p = 0.02) (Table 3).

Table 1. Annual incidence of *Plasmodium vivax* and *P. falciparum* malaria per 1,000 population in camps in Khuram Agency, Pakistan, 2002–2003

	2002		2003	
Camp	*P. vivax*	*P. falciparum*	*P. vivax*	*P. falciparum*
Ashgaroo	268.9	32.3	152.3	100.4
Bassoo	296.1	22.0	283.6	1.1
Old Bagzai	130.6	3.5	275.3	4.2
Bassoo and Old Bagzai	226.5	14.2	280.9	2.1
Remaining 6 camps	15.9	3.4	12.5	1.4

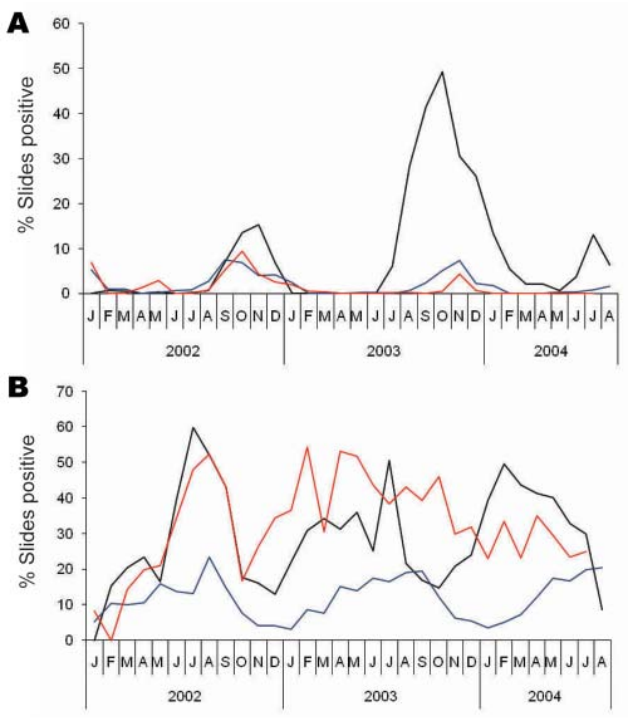

Figure 3. Slide positivity rate (% slides positive) for A) *Plasmodium falciparum* and B) *P. vivax* malaria in refugee camps in Khurram Agency, Pakistan, 2002–2004. Black lines indicate Ashgaroo camp, red lines indicate Bassoo and Old Bagzai camps combined, and blue lines indicate the remaining 6 older camps.

PCR was conducted on specimens from 81 persons; 37 samples were taken on the day of enrollment and day of treatment failure and 35 had no matching enrollment sample. All patients in whom treatment was not successful were analyzed for merozoite surface protein 2; all had recrudescent infections and not reinfections (5 samples did not yield a product). Analysis also assessed 5 loci on the *Pfdhfr* gene at positions 16, 50/51, 59, 108, and 164, and 4 loci on the *Pfdhps* gene at positions 436/437, 540, 581, and 613. Among samples matched with treatment failures, only 1 specimen showed any mutation (A16V) in the *Pfdhfr* gene. Single mutations were found in 6 of the baseline samples, but none of these polymorphisms on their own have been associated with clinical failure (*11*,*12*).

Samples of SP tablets used for routine treatment and for the drug resistance study were found to be substandard. WHO has defined substandard drugs as "the genuine drug products which do not meet quality specifications set for them. If a drug, upon laboratory testing in accordance with the specifications it claims to comply with fails to meet the specifications, then it is classified as a substandard drug." By 30 minutes of dissolution, only 52% sulfadoxine (0.156 mg/mL, n = 9) and ≈16% pyrimethamine (0.0025 mg/mL, n = 9) was detected against the stipulation that 60% (sulfadoxine 0.3 mg/mL and pyrimethamine 0.015 mg/mL) should be dissolved at this point. The dissolution profile for Fansidar met stated tolerance limits, but the locally manufactured generic tablets did not. Content analysis by HPLC showed that the generic tablets contained greater amounts of correct active ingredients (126% sulfadoxine/tablet and 128% pyrimethamine/tablet) than stated on the packaging. Because they failed to meet the criteria for dissolution tolerance, the drugs would not be released at the required dose (*13*).

Discussion

The malaria epidemic in Pakistan was intense, short-lived, and controlled by a series of active and passive interventions. Strengthening of health services, active case detection and treatment, larviciding of anopheline breeding sites, and distribution of insecticide-treated nets each played their part, although separating their individual contributions is not possible. The onset of cooler weather in November brought an end to transmission. That no excess deaths were recorded is surprising, especially with substandard first-line treatment. The well-trained health staff, a well-run and close-at-hand clinic offering free treatment, an effective second-line drug, and public awareness likely contributed to this absence of excess deaths.

A combination of factors propagated the epidemic. Digging of borrow pits provided a new habitat for vector breeding. Epidemiologic evidence suggests failure of the spray campaign. Although the Bassoo and Old Bagzai spray campaigns appear to have curtailed transmission, the failure in Ashgaroo may have been caused by several factors. Insecticide resistance would enable vector survival, but this seems unlikely because malaria was well controlled in the other sprayed camps and resistance to pyrethroids has not been observed in this region. Effective implementation of spray campaigns requires quality-assured insecticide, thorough training and supervision of spray teams, and checks on operations. The third factor may have been deficient in Ashgaroo.

In the year before the epidemic, chloroquine was used as first-line treatment despite high resistance levels (*15*). This use would enable persistence of gametocytemia in some persons and a reservoir of infection (*16*). Evidence shows that gametocytes can persist for 1 year after infec-

Table 2. Enrollment characteristics of population from in vivo drug resistance survey conducted in Ashgaroo and concurrent drug study in Yakaghund camp, Pakistan, October 2003

Characteristic	Ashgaroo	Yakaghund
No. (%) patients	169 (79.0)	45 (21.0)
% Male sex	41.8	66.7
Mean age, y (SD)	13.3 (11.9)	19.4 (13.2)
No. (%) lost to folllow-up	18 (10.7)	5 (11.1)

Table 3. Frequency of treatment failure for infection with *Plasmodium falciparum* or *P. vivax* , by group, sex, and age, Pakistan, October 2003*

Characteristic	Failure rate (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Group			
Comparison group	4/40 (10.0)	1	1
Ashgaroo	43/151 (28.5)	3.6 (1.2–10.7)	3.2 (1.0–10.1)
Sex			
M	27/90 (30.0)	1	1
F	20/99 (20.2)†	0.6 (0.3–1.2)	0.5 (0.3–1.2)
Age group, y			
0–5	16/40 (40.0)	1	1
6–10	21/72 (29.2)	0.6 (0.3–1.4)	0.6 (0.3–1.1)
11–20	4/33 (12.2)	0.2 (0.1–0.7)	0.3 (0.1–1.0)
>20	6/46 (13.0)	0.2 (0.1–0.6)	0.3 (0.1–0.8)

*OR, odds ratio; CI, confidence interval.
†Results exclude losses to follow-up.

tion (*17*). Submicroscopic gametocytemia detected by PCR indicates that the gametocyte reservoir is considerably higher than previously thought in areas of low or seasonal transmission (*18*,*19*).

In the Pakistan–Afghanistan region, only 1 epidemic has been reported recently, an outbreak of high-altitude malaria in Bamian, Afghanistan (*20*). There are similarities between that epidemic and the current one; cases were reported in June–August, when unusual environmental conditions enabled vector breeding, and population movement of infected refugees provided a source of cases into an area previously unaffected by malaria. This outbreak was circumscribed by the immune status of the affected population (nonimmune migrants) and the relative isolation of the camp.

An. subpictus mosquitoes were previously identified in the region and are competent vectors in Sri Lanka (*21*,*22*). Two studies in the Pakistan Punjab recorded peak abundance of *An. subpictus* mosquitoes in late summer and fall; the species occurred sympatrically with *An. stephensi* mosquitoes (*23*,*24*). Historically, *An. subpictus* mosquitoes are not a major vector in the Pakistan Punjab (*25*). In eastern Afghanistan, Rowland et al. (*9*) identified *An. stephensi* mosquitoes and to a lesser extent *An. culicifacies* mosquitoes as the main vectors; few *An. subpictus* mosquitoes were found by an 18-month surveillance study, and none were positive for circumsporozoite protein. *An. subpictus* mosquitoes are known to breed in muddy pools and borrow pits and later in the season than other potential vectors (*24*,*25*). Although the present study provides some evidence for *An. subpictus* being a more common vector than previously thought, it is likely that *An. stephensi* and *An. culicifacies*, the primary vector species (*9*), which were also recorded in low numbers during the surveys, played a part in transmission earlier in the summer during June and July. By September, the densities of these 2 vectors may have waned, as recorded in other longitudinal studies in eastern Afghanistan and Pakistan Punjab, but during the main transmission period were likely to have been more abundant (*9*,*23*).

Few mixed infections were seen. A recent metaanalysis (*26*) showed a negative association between *P. falciparum* and *P. vivax* but noted considerable heterogeneity related to prevalence of infection. Our data, which showed fewer *P. vivax* cases than expected in the epidemic period, indicated a suppressive effect of *P. falciparum* on *P. vivax*, as recently observed during a vector control campaign that controlled *P. falciparum* transmission but led to an increase in relapsed *P. vivax* cases (*6*).

The assessment of in vivo drug resistance was conducted in anticipation that a problem with SP resistance rather than substandard local drugs would be uncovered. Further assessments involving molecular characterization of SP resistance genes, drug quality testing, and in vivo surveys using standardized SP established that substandard drugs were the cause of what initially appeared as resistance. The drugs used routinely in the camp were procured centrally and distributed through local government organizations. A substandard drug in wide circulation will inevitably contribute to disease transmission and was undoubtedly a factor contributing to this epidemic. The substandard drugs were procured as a response to shortages. In surveys of other camps, standard SP showed a 90% cure, which indicated that low-level resistance may be an emerging problem in the study region. A distinction should be made between the more easily remedied use of poorly manufactured substandard drugs reported and the alarming growth of counterfeit drugs in Southeast Asia (*27*).

As the global prevalence of malaria decreases because of initiatives to control or eliminate the disease, more areas will become mesoendemic or hypoendemic for malaria and detection and control of epidemics will acquire greater attention. Elimination will not be easy in areas of complex emergency and population movement, and the uncontrolled production or use of substandard drugs will only add to the problem. Mechanisms to ensure quality of interventions are essential.

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Epidemiology of Hepatitis A Virus Infections, Germany, 2007–2008

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Approximately 60% of hepatitis A virus infections in Germany occur in persons without a travel history to disease-endemic areas and for whom sources of infection are unknown. Recommendation of pretravel vaccination fails to prevent the remaining imported infections. Using enhanced surveillance in 2007–2008, we analyzed epidemiologic patterns of hepatitis A in Germany and appropriateness and adequacy of current immunization recommendations. Young patients with a migration background who had visited friends and family in their ancestral countries accounted for most imported cases. Phylogenetic analysis showed high diversity of sequence data and clustering of strains with similar regions of origin or patient migration backgrounds. Virologic findings are compatible with those of low-incidence countries, where virtually all infections are directly or indirectly imported from other regions. Germans with a migration background are seen as a special risk group so far insufficiently reached by pretravel vaccination advice.

After decades of steady decreases (*1*), annual cases of hepatitis A in Germany in 2005 and 2006 remained at a relatively constant level (≈1,200 reported cases, incidence 1.5/100,000 population). The actual number of infections estimated on the basis of prevalence of immunoglobulin (Ig) G against hepatitis A virus (HAV) in Germany is presumed to be higher. Mild or subclinical infections, especially in children, are not detected by surveillance (*2*). A seasonal pattern is observed every year; most reported cases occur in late summer and fall.

In Sweden, notification data indicate that most cases are imported (*3*). However, ≈60% of reported cases in Germany occur in persons who deny recent travel to disease-endemic areas (*4*), similar to the situation in France (*5*). Exact sources and risk factors for these autochthonous infections in Germany often remain unknown because routine surveillance data lack detail.

Molecular markers, such as nucleotide sequence patterns, have proven useful for elucidating modes and chains of transmission or identifying new risk groups and factors. These factors would otherwise be difficult to determine because of the long incubation period (15–50 days) for hepatitis A and often unapparent connections between persons involved in outbreaks (*6*).

A 1-year study was initiated by the Robert Koch Institute (RKI) to characterize and compare imported and non-imported HAV infections in Germany and determine HAV genotype distribution and sources of infection. We assessed whether the virus is endemic among certain (unrecognized) risk groups, whether (and which) imported infections play a role in secondary autochthonous infections, and which population groups should be targeted for specific prevention approaches (e.g., immunization).

Methods

Routine Epidemiologic Data

The study was conducted from the 14th calendar week of 2007 through the 13th calendar week of 2008. Acute hepatitis A has been a notifiable disease in Germany for many years. Since 2001, laboratories have reported infections (test results indicative of acute HAV infection, detection of specific IgM in serum, or detection of HAV RNA in serum or feces by PCR) to local health departments. These departments collect information on case-patients (age, sex, travel history, date of onset, clinical symptoms, duration of hospitalization), take preventive measures to avoid further spread (including recommending vaccination of contacts, barring infected food handlers from working), and report standard case information electronically to state health authorities and RKI in a form in which names and addresses are removed. Data can be grouped on all levels to indicate outbreaks.

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Additional Epidemiologic Data

To transcend standard information obtained for each reported infection and add a virologic perspective, we collected additional case information on all HAV infections in Germany over a 1-year period. The 16 state health departments in Germany were requested to participate and coordinate distribution and collection of questionnaires to all local public health departments. These departments recorded additional case information obtained during routine case investigations on paper forms (additional case information sheets). Data included details of travel, concurrent health conditions, and potential migration background. These investigations consisted of telephone interviews with patients (rarely with their physicians as proxies). Completed forms were sent to RKI without names and addresses but did contain case codes. Accommodations other than hotels were defined as those presumably involving closer contact with the local population or exposure to food prepared under potentially suboptimal hygienic conditions (e.g., private accommodations, hostels, or campgrounds).

Persons with a migration background were defined as those who moved to Germany after 1949 as non-German nationals, children born in Germany to non-German nationals, or children born to at least 1 parent belonging to either of these groups. Adults were defined as persons ≥18 years of age.

Laboratory Data

We obtained serum samples from ≥10% of persons with HAV infections diagnosed in Germany during the study. To facilitate sequencing and phylogenetic analysis of a representative selection of HAV strains causing infections in Germany during the study, we asked >120 large private laboratories, university clinics, and hospitals in Germany to provide serum samples for patients for whom IgM against HAV was detected at their facilities. Samples were either sent to RKI immediately or stored at –20°C and sent in larger batches.

Collation of Data Sources

Information recorded on paper forms was entered into a database and matched to electronically transmitted routine data by case codes. All symptomatic cases reported from participating states were analyzed. Clinical specimens were matched to questionnaire and surveillance data according to anonymous patient information (year and month of birth, sex, crude area of residence, date of blood sampling) provided by the laboratories.

Isolation and Sequencing of HAV RNA

HAV RNA was isolated from serum samples by using a Viral RNA Mini Kit (QIAGEN, Hilden, Germany). Reverse transcription and first-round amplification of the capsid protein (VP1)/2A junction region of HAV were performed by using a Onestep RT-PCR Kit (QIAGEN) and primers (Table 1).

Nested PCR was performed by using the HotStarTaq Master Mix Kit (QIAGEN). Purified products of the nested PCR (forward and reverse strands) were sequenced by using a 3130x ABI Prism Genetic Analyzer and a BigDye Terminator version 3.1 Cycle Sequencing Kit (PE Applied Biosystems, Weiterstadt, Germany).

Statistical Analysis

Sequences were processed by using Lasergene SeqMan Pro software (DNASTAR, Inc., Madison, WI, USA), aligned by using the ClustalW algorithm (*7*), and optimized manually. Phylogenetic trees were constructed by using all available HAV sequences from obtained HAV IgM–positive samples (including HAV sequences from cases not reported). Sequence statistical and phylogenetic analyses were conducted by using MEGA4 (*8*). Sequences obtained are referenced in GenBank under accession nos. EU416232–EU416273 and EU825848–EU825918. For statistical analysis, we used Microsoft Excel 2003 (Microsoft, Redmond, WA, USA), SPSS version 15.0 (SPSS Inc., Chicago, IL, USA), and STATA version 10.1 (StataCorp, College Station, TX, USA).

Results

Study Population

A total of 1,213 HAV infections were reported. Among them, 952 (78.5%) were in patients with clinical symptoms consistent with acute hepatitis A. Of the 16 states in Ger-

Table 1. Primers used for detection of HAV RNA by nested RT-PCR in clinical specimens from patients in Germany, 2007–2008*

Primer	Sequence (5′ → 3′)	Orientation, position, and use
HAV6a	GGA AAT ATT CAG ATT AGG YTG CCT TGG T	Sense, 2793–2820, reverse transcription and first-round PCR
HAV6b	GGG AAC ATT CAG ATY AGA TTG CCW TGG T	
HAV17a	CAA AGC TCT AGT RTC AGC AGT AAT TCC	Antisense, 3300–3326, reverse transcription and first-round PCR
HAV17b	CAA AGC CCT AGT RTC AGC AGT CAC TCC	
HAV8a	CTT TTG GAT TKG TTT CYA TTC AGA TTG C	Sense, 2882–2908, nested PCR and sequencing
HAV7a	GAA AAC TTC ATT ATT TCA TGM TCY TCW GT	Antisense, 3264–3292, nested PCR and sequencing

*HAV, hepatitis A virus; RT-PCR, reverse transcription–PCR. Positions in the HAV genome are given according to strain HM-175 (GenBank accession no. M14707).

many, 13 participated in the intensified surveillance and contributed 1,037 (85.5%) of all reported infections and 816 (86%) of all reported symptomatic cases (maximal denominator for analysis). Additional case information sheets were available for 571 (70%) symptomatic cases. Serum samples positive for IgM against HAV were available for 189 (23.2%) cases; 95 (11.6%) were PCR positive.

A total of 74.6% of the cases were reported as single cases; the remainder were in recognized clusters. Among case-patients, 47.1% were male (Table 2); age range <1 to 90 years (median 32 years). Among nonadults, 81.1% were reported to have had jaundice. Among adults, the proportion of persons with jaundice decreased with age to 40.6% in persons ≥60 years of age.

Of case-patients, 46.4% were hospitalized for a median of 6 days (range 1–28 days). Among those with jaundice, no clear trend for age was found in 50.2% who were hospitalized. Among those without jaundice, the proportion of those hospitalized increased among persons ≥60 years of age (56.5%) when compared with that of younger persons (31.3%, relative risk [RR] 1.81, 95% confidence interval [CI] 1.35–2.41). Among those employed, absences from work ranged from 2 to 32 work days (median 6 days).

Overall, 43.6% of the infections were imported (i.e., infection acquired while traveling outside Germany). Nonadults (60.6% imported; $p<0.001$) and male patients (48.1% imported; $p = 0.018$) were overrepresented.

A migration background was reported by 42.2% of case-patients (78.8% of nonadults and 19.1% of adults), of whom 64.8% had been born in Germany. Among migration backgrounds, Turkey was reported most frequently (48.5%), followed by the former Yugoslavia (11.9%), southern and Southeast Asia (9.7%), and the former USSR (8.8%). Nonadults with a migration background lived with a larger number of household members (range 1–11 persons in addition to the case-patient, median 4) than those without a migration background (range 1–6 persons, median 3). Among adult case-patients, 5.2% were professional food handlers.

Imported Infections and Comparison with Autochthonous Infections

Among known destinations, Turkey (35.6%) was reported most frequently, followed by the former Yugoslavia, Egypt, and Spain (Table 3). Most affected case-patients (63.9%), especially nonadults (82%), had not traveled for vacation or business but had visited friends or family. Median duration of travel preceding infection was 29 days (range 1–180 days). Accommodations other than hotels (e.g., staying with friends or family) predominated (73.1%), especially among those visiting Turkey (91.9%) and the former Yugoslavia (94.1%). A total of 92.9% of those infected in Turkey and 76.2% of those infected in countries of the former Yugoslavia had matching migration backgrounds; only 3 (16.7%) of those infected in Egypt had matching migration backgrounds. Of case-patients with migration backgrounds who had become infected in these ancestral countries, 75.9% from Turkey, 87.5% from the former Yugoslavia, and 100% from Egypt were nonadults.

Imported infections were most likely to cause disease from August through October, and a prolonged wave of autochthonous infections then followed from October through March (Figure 1). Among imported infections, children and persons <20 years of age were overrepresented, (70.2% from August through October vs. 33.9% in other months; $p>0.001$). Among autochthonous cases, incidence in children and persons <20 years of age increased 62% from September through February compared with March through August. Autochthonous cases in adults ≥40 years of age were almost evenly spread throughout the year.

Table 2. Characteristics of 816 patients tested for hepatitis A virus infection, Germany, 2007–2008

Characteristic	No. (%) patients	No. (%) patients with additional case information	No. (%) patients with serum samples available
Sex			
M	384 (47.1)	266 (46.7)	101 (53.7)
F	431 (52.9)	304 (53.3)	87 (46.3)
Age, y			
<1–9	168 (20.6)	136 (23.9)	44 (23.3)
10–19	138 (16.9)	107 (18.8)	32 (16.9)
20–39	157 (19.3)	119 (20.9)	43 (22.8)
40–59	180 (22.1)	116 (20.4)	39 (20.6)
≥60	172 (21.1)	92 (16.1)	31 (16.4)
Hospitalized			
Yes	377 (46.4)	266 (46.6)	87 (46.3)
No	436 (53.6)	305 (53.4)	101 (53.7)
Imported infection			
Yes	346 (43.6)	269 (47.1)	89 (47.8)
No	447 (56.4)	302 (52.9)	97 (52.2)

Table 3. Travel characteristics of 346 patients infected with hepatitis A virus, Germany, 2007–2008

Characteristic	No. (%) patients
Destination	
Turkey	89 (35.6)
Former Yugoslavia	24 (9.6)
Egypt	18 (7.2)
Spain	15 (6.0)
Pakistan	10 (4.0)
Morocco	7 (2.8)
Others	86 (34.5)
All	249 (99.7)
Duration of travel, d	
1–14	51 (22.7)
15–29	62 (27.6)
30–180	112 (49.8)
All	225 (100)
Type of travel	
Visiting friends or family	149 (63.9)
Other Vacation	79 (33.9)
Business	5 (2.1)
All	233 (100)
Type of accommodation	
Private	141 (73.1)
Hotel or cruise ship	52 (26.9)
All	193 (100)

Case-patients with autochthonous infections were older than case-patients with imported infections and less likely to have migration backgrounds (Figure 2). Almost all patients ≥60 years of age had autochthonous infections.

A migration background was more likely among persons with imported infections; 52.8% of case-patients had a background of migration from Turkey. However, 23% of persons with autochthonous infections had a migration background (Table 4). Patients with autochthonous infections were older; 56.4% persons with nonimported cases were ≥40 years of age and 31.1% were ≥60 years of age, compared with only 24% and 7.5%, respectively, of persons of the same ages with cases of imported infections. Case-patients with imported infections were also slightly more likely to be male and part of case clusters than were autochthonous case-patients.

Close contacts of 58.4% of the patients received prophylactic vaccinations (range 1–150 persons, median 3). Contacts were more frequently vaccinated in response to cases in nonadults (RR 1.594, 95% CI 1.374–1.849).

No large outbreaks were reported during the study. In the 13 participating states, 9 clusters with ≥5 infections were detected. The largest (13 symptomatic and 2 asymptomatic infections) was in a school with multiple generations of infection. The ultimate source of infection could not be elucidated. The school index case-patient had not traveled. However, the implicated HAV strain was genetically similar to strains from Turkey. In 4 of the 8 outbreaks with 5–7 infected persons, ≥1 travel-associated index cases were recognized, leading to 1–4 secondary infections in Germany.

Detection of HAV RNA

HAV RNA was detected in 95 (50.3%) of 189 samples matching a reported case of symptomatic HAV infection. The likelihood of detecting HAV RNA in serum depended on clinical characteristics of patients (Table 5). Frequency of RNA detection increased with number of symptoms

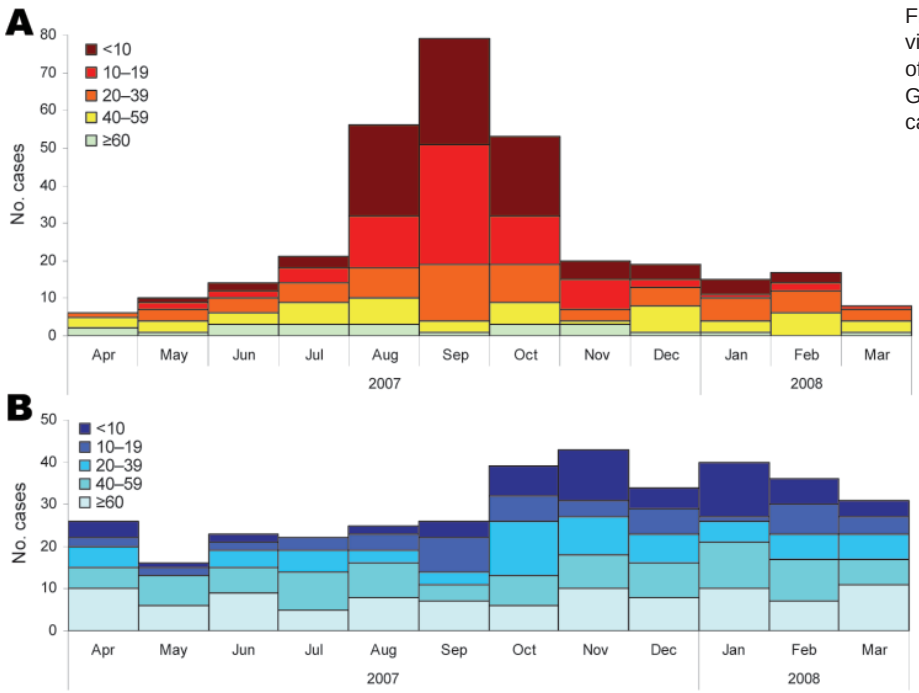

Figure 1. Reported cases of hepatitis virus A infection (n = 679) by month of onset and patient age group (y), Germany, 2007–2008. A) Imported cases. B) Nonimported cases.

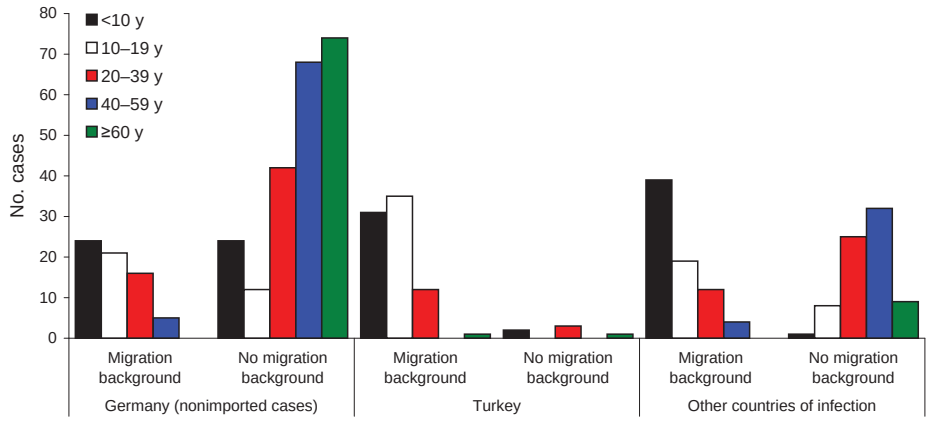

Figure 2. Age distribution (y) of persons with hepatitis A virus (HAV) infection by migration background and country where HAV infection was acquired (n = 520 with all 3 factors known), Germany, 2007–2008.

reported (p<0.02) and was negatively associated with patient age (p<0.001). Although this frequency was similar for nonadults and adults ≤39 years of age (mean 65%), RNA was detected in only 10% of symptomatic patients ≥60 years of age. No correlation was seen between duration from symptom onset to day of blood sampling (maximum 29 days) and positive results for HAV RNA.

Molecular Epidemiology

A PCR-generated 348-bp fragment was available for analysis of isolates with detectable HAV RNA from 126 patients. Of these patients, 73 (57.9%) had genotype IB strains, 36 (28.6%) had genotype IA strains, and 17 (18.6%) had genotype IIIA strains. Sequences differed in ≤8.9%, ≤7.5%, and ≤4.9% of positions within genotype IB, IA, and IIIA strains, respectively. Sequence variability was reflected in the diversity of countries or regions from which sequences originated (Figure 3).

Phylogenetic analysis showed that imported strains clustered according to region or country. Imported genotype IB strains were isolated from patients who traveled to Turkey, the Middle East, and Africa. Strains acquired in South Africa formed a small but distinct subcluster. Patients infected with genotype IA strains reported traveling to eastern Europe, Asia, South America, and northwestern Africa. The small number of imported genotype IIIA strains was obtained from patients who had traveled to eastern and southeastern Europe and Central and southern Asia. Three strains imported from Spain (2 genotype 1A and 1 genotype 3A) were genetically more distant from each other than to strains from other regions (e.g., northern Africa).

Strains from patients with known migration backgrounds (Figure 3) but no travel histories clustered with imported strains of the respective region. This finding was evident in a clade containing 35 highly related genotype IB strains, of which 14 were imported from Turkey. Of 23 persons with a background of migration from Turkey and for whom sequence data were available, 18 (78%) were infected with strains that were found within this clade. Furthermore, among persons who traveled to Turkey and available information on possible migration background (n = 12), all also had a background of migration from Turkey. Strains isolated from patients with autochthonous infections but without known migration backgrounds were nearly as genetically diverse as imported strains. Individual autochthonous strains, however, were frequently very homogeneous to individual imported strains.

Most (53.2%) HAV sequences obtained were found only once. Another 18.3% were isolated from smaller outbreaks of hepatitis A, which had already been detected through routine surveillance (Figure 3). Remaining sequences (28.6%) were each seen 2 or 3 times without any known epidemiologic connection. The exception was a strain found in 12 patients who represented sporadic cases and smaller outbreaks. This strain is part of the clade from Turkey mentioned earlier; among autochthonous cases with this strain, no clustering of time or place of infection was apparent.

Table 4. Characteristics of patients with imported and nonimported hepatitis A virus infections, Germany, 2007–2008*

Characteristic	No. (%) patients with imported infections	No. (%) patients with nonimported infections	Total no. (%) infected patients	RR (95% CI)
Migration background	161 (63.9)	66 (23.0)	227 (42.1)	2.43 (2.01–2.95)
Male sex	180 (52.0)	194 (43.5)	374 (47.2)	1.21 (1.04–1.42)
Age <18 y	169 (48.8)	110 (24.7)	279 (35.2)	1.76 (1.51–2.04)
Age ≥60 y	26 (7.5)	140 (31.4)	166 (21.0)	0.31 (0.21–0.44)
Part of case cluster	79 (29.5)	65 (21.8)	144 (25.4)	1.22 (1.00–1.49)
<18 y of age with migration background	119 (91.5)	45 (57.7)	164 (78.8)	2.90 (1.73–4.88)

*RR, relative risk; CI, confidence interval.

Table 5. Serum samples positive for hepatitis A virus RNA by patient and disease characteristics for reported cases with symptomatic infections, Germany, 2007–2008

Characteristic	No. samples, n = 189	No. (%) positive samples, n = 95
Patient age, y		
<1–9	44	30 (68)
10–19	32	20 (63)
20–39	43	28 (65)
40–59	39	14 (36)
≥60	31	3 (10)
Sex		
M	102	55 (54)
F	87	40 (46)
Signs and symptoms		
Abdominal pain	83	40 (48)
Fever	73	45 (62)
Jaundice	115	69 (60)
Increased transaminase levels	83	39 (47)
No. above items reported		
1	53	27 (51)
2	98	43 (44)
3	27	20 (74)
4	6	5 (83)
Probable place of infection		
Germany	115	49 (43)
Abroad	69	44 (64)

Discussion

Detailed epidemiologic data for 70% of symptomatic cases reported in participating states during the study (60% of all cases) enabled us to characterize incident cases of HAV infection in Germany better than using routine surveillance data alone. Although deaths from hepatitis A are rare, frequent hospitalization and work time missed by patients or adults caring for sick children emphasize the need to focus on hepatitis A.

Despite existing vaccination recommendations for travelers to countries with high or intermediate levels of endemicity for hepatitis A, >40% of cases were directly related to travel. Among these cases, persons with any migration background were overrepresented, especially those who had a background of migration from Turkey. The German Statistical Office in 2006 reported that 16% of adults and 26% of children (overall 19%) living in Germany had a migration background, compared with 63.9% of our patients with imported cases. Among those with a migration background who lived in Germany, 22% were from Turkey (9), but 48.5% of the case-patients had a Turkish migration background.

Among persons with infections imported from Turkey, 92% had a migration background even though Turkey is also a popular travel destination for persons from Germany without a migration background. These findings are consistent with surveillance data from Denmark, which show that 80% of travel-associated hepatitis A cases during 2002–

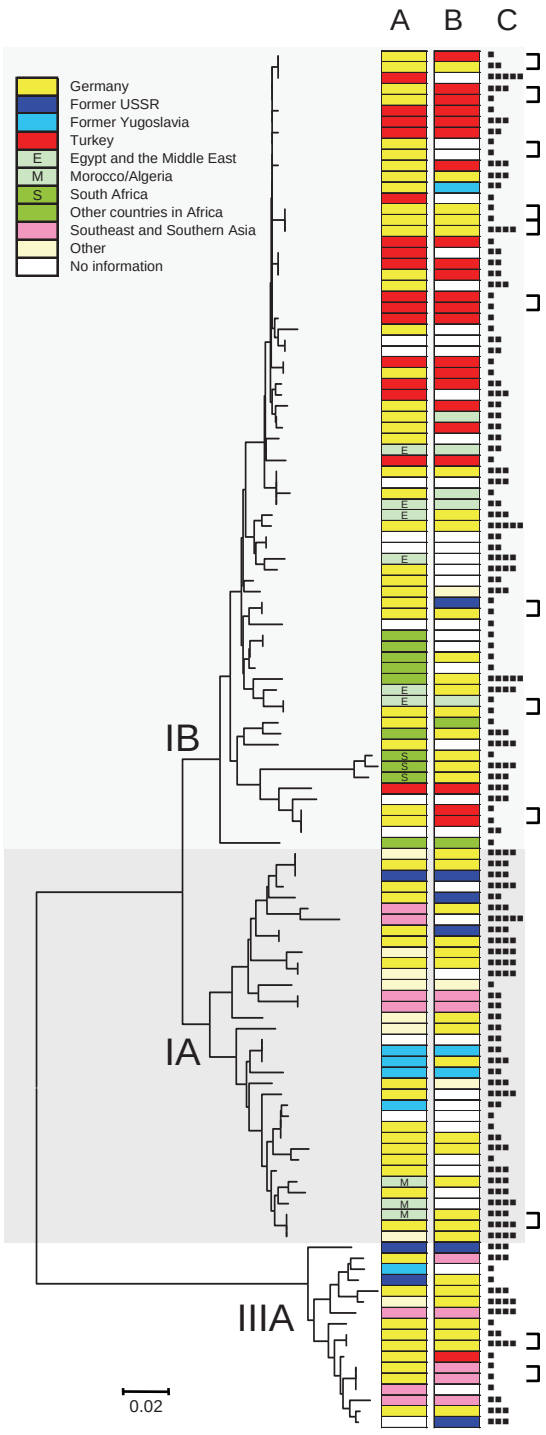

Figure 3. Neighbor-joining phylogenetic tree of a 348-bp section of the viral capsid protein 1//2A junction region of hepatitis A virus (HAV) constructed by using the Kimura 2-parameter distance model. Place of infection (A), migration background (B), and age of case-patients (■, 0–9 y; ■■, 10–19 y; ■■■, 20–39 y; ■■■■, 40–59 y; ■■■■■, ≥60 y) (C) are shown for each HAV isolate. Linked cases as judged by health departments are indicated by brackets. HAV subgenotypes are indicated by roman numerals and letters. Scale bar indicates nucleotide substitutions per site.

2006 occurred in immigrants or children of immigrants, of whom 78% had acquired the disease while visiting their ancestral country (*10*).

Persons who travel to visit friends and family abroad are at greater risk for many preventable infectious diseases than persons traveling for other purposes, such as tourism (*11*). This higher risk for patients with migration backgrounds may be associated with regions visited. For example, persons who live on the Aegean coast of Turkey have lower prevalences of antibodies against HAV, which is indicative of the current level of HAV circulation, than do persons who live in eastern Anatolia, where many immigrant families have their roots (*12*).

Travelers who had stayed at private lodgings, visited friends or family, and traveled longer appeared to be overrepresented among cases. This result is supported by several studies, which demonstrated that persons planning visits to friends and relatives are less likely than other travelers to be vaccinated against HAV (*13–15*). Low vaccination coverage may be caused by lack of awareness by patients and physicians that when visiting friends and family in a hepatitis-endemic area, a vaccination before travel is recommended. Older persons with migration backgrounds may be immune to HAV because of previous exposure during childhood in their country of origin, but younger persons with migration backgrounds require vaccinations to acquire immunity. Persons with migration backgrounds, similar to friends and relatives they are visiting, may not be aware of hepatitis A because in many areas to which this disease is endemic, most infections occur in early childhood, and hepatitis A is rarely detected. Lower food safety standards for home cooking and contact with children in whom the virus circulates may facilitate acquisition of HAV by travelers when they stay with friends and family.

Population groups with a higher risk for acquiring HAV infection abroad are also more likely to acquire secondary infections. Molecular and questionnaire data showed that geographic origin of HAV strains most often matched the origin of patients with imported and autochthonous cases. These findings indicate that cases are imported by persons who visit home countries and that at least limited autochthonous spread of cases occurs among close contacts. Children of migrants born and raised in countries with low incidences of hepatitis A and who have no previous exposure and immunity to HAV can facilitate introduction of HAV into large households and the general community through schools or childcare facilities (e.g., outbreaks in Denmark [*16*] and the Netherlands [*17*]). In the Netherlands, hepatitis A immunization campaigns specific for children traveling to hepatitis A–endemic areas have proven to be useful for reducing the incidence of HAV infections among persons with migration backgrounds and others (*18*). Using vaccination to protect those at risk for primary infections while abroad would also preclude secondary spread in Germany.

Phylogenetic analysis of HAV sequences obtained showed a greater diversity of strains than that reported in a similar study in Amsterdam, the Netherlands (*19*). The 3 major genotypes were found in Germany. Within these genotypes, only limited relatedness but many unique strains were observed. As described in another study, HAV strains clustered according to geographic origin. This pattern is compatible with patterns from countries with a low incidence of HAV, where no or limited transmission occurs outside risk groups and most infections are caused by importation from areas outside the countries (*20*).

The largest cluster of strains observed was that of several highly related genotype IB strains. This cluster included only strains from cases imported from Turkey or nonimported cases from patients with a background of migration from Turkey. These strains were obtained throughout Germany during several months. Thus, relatedness may reflect endemicity to Turkey rather than endemic spread among a specific population in Germany.

Lack of distinct clusters containing predominantly autochthonous cases suggests that supraregional, unrecognized outbreaks did not occur during the study. Although infections secondary to imported cases may be frequent, especially in the immediate vicinity (household, family) of a case-patient, infection chains quickly terminate. This finding is also likely to result in part from satisfactory hygienic conditions in Germany but is also likely a result of effective tracing and vaccination of case-contacts by local health departments. Although the exception, larger outbreaks in daycare centers (*21*), those caused by food products (*22*), and those among men who have sex with men (*23*) are likely to be detected through routine surveillance. The largest outbreak detected in Germany in recent years involved tourists who had stayed at the same hotel in Egypt and was caused by consumption of contaminated orange juice (*24*).

The results of our study also provide information on specificity of surveillance data. Especially among older hospitalized patients, frequently without jaundice, IgM-positive serum samples were mostly negative for HAV RNA, which suggests false-positive serologic results. HAV IgM–positive samples that showed negative results by reverse transcription–PCR probably showed false-positive HAV IgM results for patients with persisting HAV IgM (*25*), cross-reactions in the test (e.g., in acute-phase infections with Epstein-Barr virus [*26*]), or nonspecific polyclonal activation of memory cells (*27*). As a bias favoring stability, this overestimate of numbers of cases has limited consequences for surveillance purposes. However, for the individual patient, specificity of IgM in serum samples should be strongly considered.

The main conclusion of this study is that existing vaccination recommendations for travelers to areas endemic for hepatitis should be emphasized. Furthermore, immunization of travelers should be made more accessible to risk groups through information campaigns and removal of financial barriers (insurance payments for pretravel advice and vaccinations are not universal). If removal of these barriers to vaccination of all travelers is unlikely, the general vaccination of children against HAV should be considered, given the high number of imported infections among children and the evidence of secondary autochthonous transmission.

Efforts to communicate recommendations to previously unaware population groups, especially, but not exclusively, persons with migration backgrounds, have the capacity to strongly reduce the number of HAV infections in Germany. However, as long as vaccination recommendations are applied only to travelers and overall immunity in the population remains low or decreases further, risk for secondary transmission of imported infections remains high.

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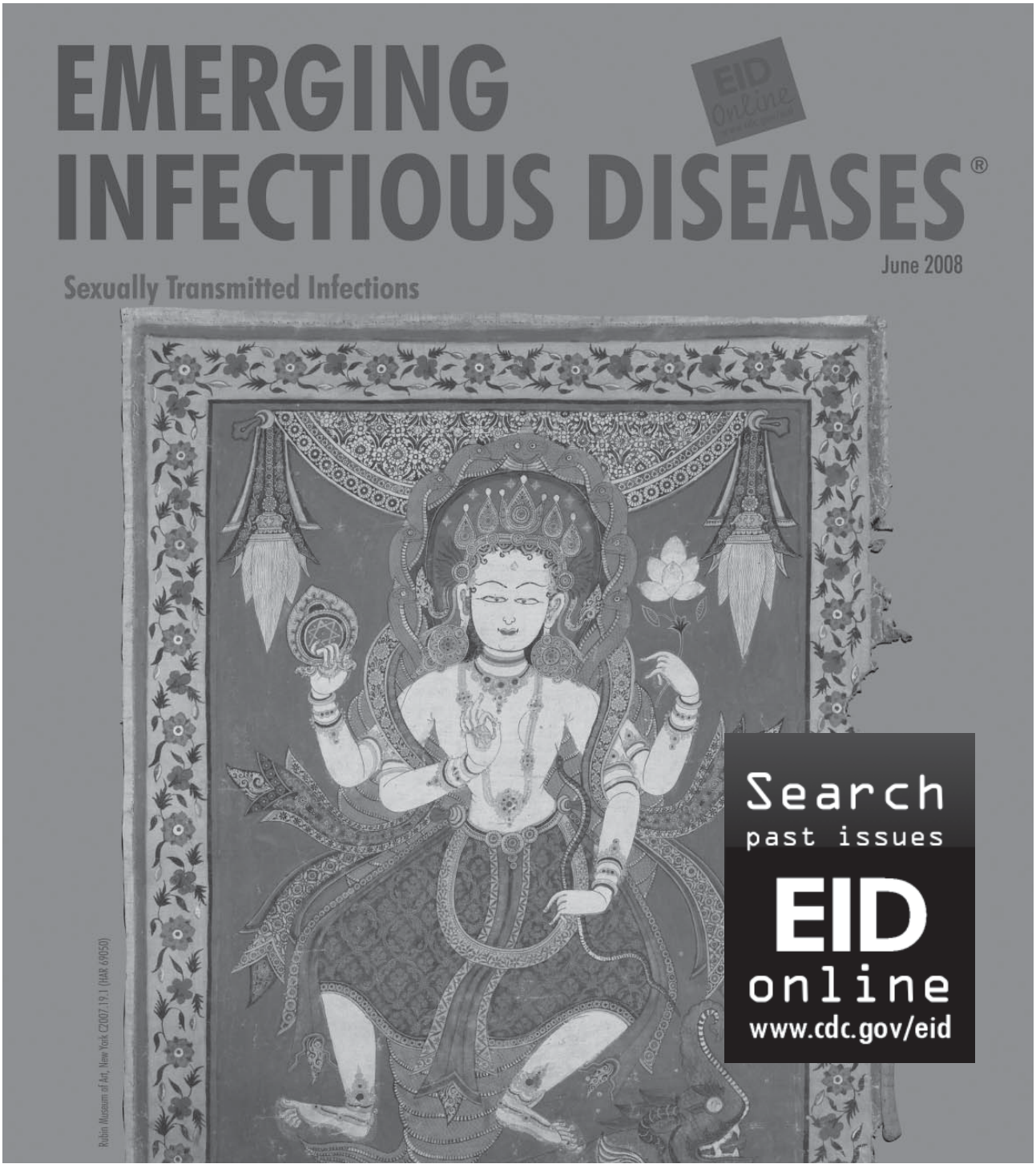

Screening Practices for Infectious Diseases among Burmese Refugees in Australia

Nadia J. Chaves,[1] Katherine B. Gibney,[1] Karin Leder, Daniel P. O'Brien, Caroline Marshall, and Beverley-Ann Biggs

Increasing numbers of refugees from Burma (Myanmar) are resettling in Western countries. We performed a retrospective study of 156 Burmese refugees at an Australian teaching hospital. Of those tested, *Helicobacter pylori* infection affected 80%, latent tuberculosis 70%, vitamin D deficiency 37%, and strongyloidiasis 26%. Treating these diseases can prevent long-term illness.

Burma (Myanmar) has been the most common country of origin for refugees who have recently resettled in the United States and Australia (*1*,*2*). Before resettling in Australia, most refugees undergo testing for HIV, have a chest radiograph to exclude active tuberculosis (TB), and may undergo other testing, depending on exposure risk. Many refugees also receive a health check and treatment for malaria and stool parasites within 72 hours of departure for Australia (*3*,*4*). Most refugees who resettle in Victoria, Australia, are screened by primary care doctors and then referred to specialist clinics as appropriate.

In this study, we examined the effect of illness and the adequacy and completeness of health screening among Burmese refugees referred to the infectious diseases clinic of an Australian tertiary hospital during a 5-year period.

Methods

We performed a retrospective cohort study of all Burmese refugees who attended the Victorian Infectious Diseases Service outpatient clinics at the Royal Melbourne Hospital, Australia, during January 1, 2004–December 31, 2008. Patients were identified through the hospital registration database, and medical, pathologic, radiologic, and pharmacologic records were reviewed. Screening tests audited included those suggested by the Australasian Society for Infectious Diseases refugee screening guidelines (*5*), along with vitamin D and hematologic studies. These latter tests included full blood count, mean corpuscular volume, and platelet count. Investigations were performed at the discretion of the treating doctor, and not all tests were performed for each patient. Time was calculated from time of arrival in Australia to first clinic attendance. The results of serologic tests and QuantiFERON-TB Gold tests (QFT-G; Cellestis Limited, Carnegie, Victoria, Australia), were interpreted according to the manufacturers' recommendations.

Conditions were defined according to prespecified criteria as follows: schistosomiasis; strongyloidiasis; HIV and syphilis (positive serologic test results); hepatitis C virus (RNA detected by PCR); *Helicobacter pylori* (positive results for fecal antigen test, carbon-14 breath test, or serologic analysis); malaria (thick and thin blood films or immunochromatographic test result positive for *Plasmodium* species); chlamydia and gonorrhea (DNA detected by PCR in first-pass urine); active TB (microbiologic or histologic evidence of *Mycobacterium tuberculosis* infection or receiving treatment for active TB during the study period); latent TB infection (Mantoux test result $\geq$10 mm or positive QFT-G result and no clinical evidence of active disease); chronic hepatitis B virus (HBV; hepatitis B surface antigen detected); isolated core antibody against HBV (hepatitis B core antibody detected, hepatitis B surface antibody and hepatitis B surface antigen not detected); pathologic

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stool parasites (stool microscopy positive for a pathogenic species); vitamin D deficiency (serum 25[OH] vitamin D level <50 nmol/L); anemia (hemoglobin level <120g/L); and eosinophilia (eosinophil count >0.4 × 10^9 cells/L). The Melbourne Health Human Research Ethics Committee approved this study as a quality assurance audit.

Results

A total of 156 Burmese refugees were referred to the infectious diseases outpatient clinics at the Royal Melbourne Hospital during the study period. Table 1 summarizes the characteristics of these patients. Median age was 30 years (range 16–86 years); approximately half were male (51%) and of Karen ethnicity (48%). Most refugees were born in Burma (97%) and had spent time in a refugee camp (97%). The proportion of these patients who were screened according to the Australian refugee health guidelines is shown in the Figure. More than 90% of study patients were tested for 6 diseases (*Mycobacterium* TB, HIV, hepatitis B, hepatitis C, schistosomiasis, and *Strongyloides stercoralis* infection).

Table 2 shows the prevalence of selected medical conditions in this patient group. Chronic HBV infection was found in 14% of the group; isolated core antibody against HBV was found in 13%. Hepatitis B DNA was not detected in the serum of any patients with isolated core antibody against HBV. One person had HIV infection; this person had a chronic infection with HBV. *H. pylori* infection was identified in 80% of those tested (7 persons by carbon-14 breath test, 7 by fecal antigen test, and 19 by serologic analysis). No cases of multidrug-resistant TB were found.

Eosinophilia was documented in 35% of those tested, 47% of whom had strongyloidiasis, 4% schistosomiasis, and 24% a pathologic stool parasite, that causes eosinophilia. Eosinophilia was not explained by these conditions in 33%.

Discussion

In recent years, an increasing number of refugees from Burma have resettled in Australia, North America, and Europe. This study reports high rates of *H. pylori* infection (80%), latent TB infection (70%), vitamin D deficiency (37%), and strongyloidiasis (26%) in Burmese refugees attending the infectious diseases clinics of a Melbourne tertiary referral hospital.

A Canadian study of 68 Karen refugees, more than half of whom were <18 years of age, appears to be the only previously published study on the health status of Burmese refugees settled in a Western country (*6*). One unpublished study found on the Internet was conducted by the Minnesota Department of Health, which examined 159 Burmese migrants, but no demographic information was included (*7*). We have compared our screening results with those of these 2 studies in Table 2.

Table 1. Patient characteristics, Burmese refugees in Australia, 2004–2008*

Characteristic	Value
Age group, y, no. (%)	
<25	36 (23.1)
25–49	108 (69.2)
≥50	12 (7.7)
Gender, no. (%)	
M	80 (51.3)
F	76 (48.7)
Country of birth, no. (%)	
Burma (Myanmar)	152 (97.4)
Thailand	4 (2.6)
Preferred language, no. (%), n = 155	
Burmese	23 (14.8)
Karen	74 (47.7)
Chin	55 (35.5)
English	2 (1.3)
Zotung	1 (0.6)
Transit through refugee camp, no. (%), n = 137	133 (97.1)
Country of refugee camp, no. (%), n = 135	
Thailand/Thailand-Burma border	71 (52.6)
Malaysia	55 (40.7)
Other	9 (6.7)
Referral by general practitioner, no. (%)	151 (96.8)
No. clinic visits per refugee, median (range)	5 (1–18)
No. months attended clinic, median (range)	8 (1–23)
No. months in Australia, median (range)	4 (<1–60)

*n = 156 unless otherwise specified.

A high rate of parasitic intestinal infections has been documented in refugees from Burma in Thailand (*8–10*) and North America (*6*,*7*), and our findings are consistent with these studies. Parasitic intestinal infections were common in our study despite some refugees reporting that they had received predeparture drug therapy with albendazole. Therefore, we suggest that refugees migrating from Burma to Australia who underwent postarrival stool evaluation may not have received the predeparture antiparasitic, or if received, the treatment was ineffective. Moreover, infec-

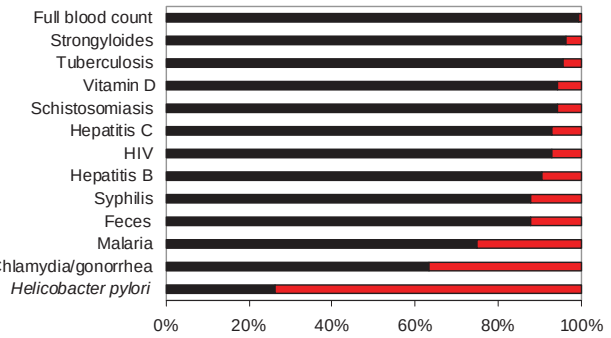

Figure. Proportion of 156 recently arrived Burmese refugees with documented screening tests for common health conditions, Australia, 2004–2008. Most of these tests are recommended by the Australasian Infectious Diseases Society guidelines (*5*). Tests for vitamin D levels are beyond the scope of these guidelines. Black, tested; red, not tested.

Table 2. Proportion of patients with selected conditions compared with other studies of Burmese immigrants, retrospective cohort study, Australia, 2004–2008*

Condition	This study, no. positive/ no. tested (%), N = 156	Denburg study (*6*), % positive, N = 68	Minnesota Department of Health study (*7*), % positive, N = 159
Helicobacter pylori infection	33/41 (80.5)		
Latent TB	105/149 (70.5)	28	52
Vitamin D deficiency	55/147 (37.4)		
Eosinophilia	55/155 (35.5)	50	
Strongyloides infection (serology)	39/150 (26.0)	7.5	
Stool parasites (pathology)	33/137 (24.1)	32	18
Chronic HBV infection	20/141 (14.2)	13	9
Isolated core antibody against HBV	18/141 (12.8)		
Schistosomiasis (serology)	8/147 (5.4)		
HCV infection	4/145 (2.8)		
Active TB	3/149 (2.0)		
Syphilis	2/137 (1.5)	0	<1
Malaria	1/145 (0.7)		
HIV infection	1/117 (0.9)		
Chlamydia infection/gonorrhea	0/99 (0.0)		

*TB, tuberculosis; HBV, hepatitis B virus; HCV, hepatitis C virus.

tion with *S. stercoralis* was common in this study. This parasite is unlikely to be eradicated with only 1 dose of albendazole and is associated with chronic complications, including hyperinfection syndrome and death (*11*).

The rate of infection with *H. phylori* in this group was surprisingly high at 80%, although the numbers of refugees tested was small and those tested were symptomatic. High rates of infection with *H. phylori* have been seen in other immigrant groups (*12*,*13*). This result reinforces the need to question refugees regarding dyspeptic symptoms and to test those with symptoms because of established links between *H. pylori* infection and iron deficiency, peptic ulcer disease, and gastric cancer (*14*,*15*).

National screening protocols for refugees were closely followed in this study for most infectious diseases. Lower compliance (≤88%) with screening protocols was reported for malaria, chlamydia, and gonorrhea. However, these conditions were uncommon in this group. Ongoing education of health professionals who care for refugees is required to encourage more complete screening of refugees.

This study has a number of limitations. A relatively small number of patients were tested. Because this study was retrospective and screening was incomplete for some patients, certain diseases may be underestimated, or if testing was based on symptoms rather than true screening, diseases may be overestimated. Some conditions will be overrepresented because of referral bias and because certain tests (e.g., for *H. pylori*) were performed as diagnostic evaluation of symptomatic patients. This study highlights the difficulties in providing complete health screening for refugees, outlines the range of health problems among Burmese refugees referred to an adult tertiary hospital in Australia, and reinforces the high prevalence of treatable conditions in refugee communities.

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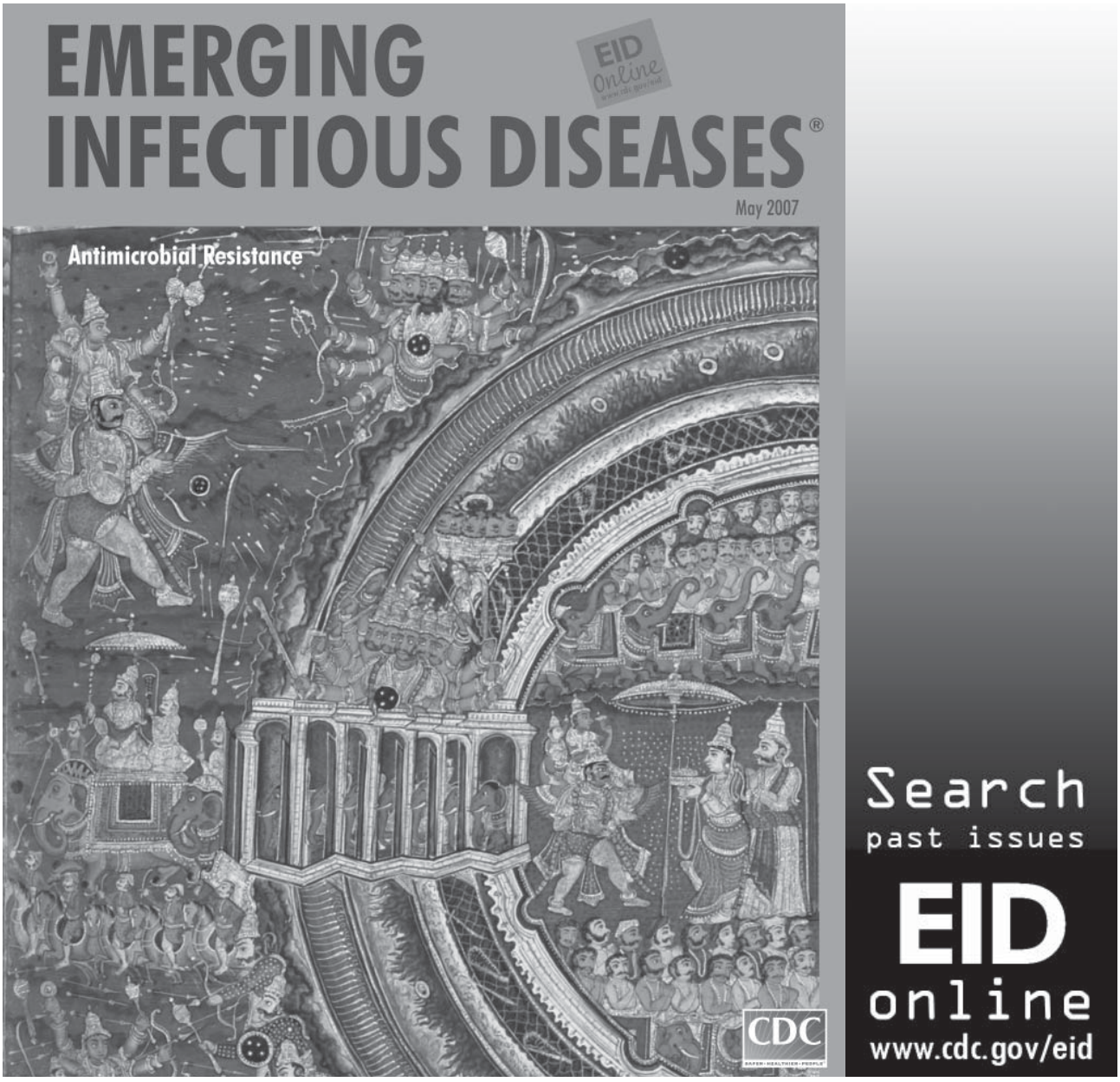

Illness in Long-Term Travelers Visiting GeoSentinel Clinics

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Length of travel appears to be associated with health risks. GeoSentinel Surveillance Network data for 4,039 long-term travelers (trip duration >6 months) seen after travel during June 1, 1996, through December 31, 2008, were compared with data for 24,807 short-term travelers (trip duration <1 month). Long-term travelers traveled more often than short-term travelers for volunteer activities (39.7% vs. 7.0%) and business (25.2% vs. 13.8%). More long-term travelers were men (57.2% vs. 50.1%) and expatriates (54.0% vs. 8.9%); most had pretravel medical advice (70.3% vs. 48.9%). Per 1,000 travelers, long-term travelers more often experienced chronic diarrhea, giardiasis, *Plasmodium falciparum* and *P. vivax* malaria, irritable bowel syndrome (postinfectious), fatigue >1 month, eosinophilia, cutaneous leishmaniasis, schistosomiasis, and *Entamoeba histolytica* diarrhea. Areas of concern for long-term travelers were vector-borne diseases, contact-transmitted diseases, and psychological problems. Our results can help prioritize screening for and diagnosis of illness in long-term travelers and provide evidence-based pretravel advice.

Travelers have many reasons for long durations of travel, including diplomatic work, education and research, missionary work, Peace Corps volunteer (PCV) work, military operations, backpacking trips, and corporate expatriate assignments (*1*–*7*). Longer trips often are assumed to be associated with increased risk for some health problems, but few studies have compared the types and causes of illness in travelers on the basis of duration of travel. Previous studies suggested that long-term travelers are more likely than short-term travelers to acquire malaria (*8*) and that recommendations should be tailored individually (*9*). Other illness also might be more common in long-term than in short-term travelers.

To evaluate the effect of trip duration on illness, we compared illnesses by duration of travel for travelers seeking treatment at GeoSentinel Surveillance Network sites. We also characterized long-term travelers' demographics, travel patterns, and travel-related illnesses.

Methods

GeoSentinel Surveillance Network (www.istm.org/geosentinel/main.html) sites are clinics on 6 continents that specialize in travel or tropical medicine and contribute data on travel-related illnesses and trip information. Our study comprised data from ill travelers visiting GeoSentinel sites from June 1, 1996, through December 31, 2008.

Inclusion Criteria

Persons in our study must have crossed an international border within the past 10 years and then sought treatment or medical advice at a GeoSentinel site for a presumed travel-related illness. Only travelers with confirmed and probable diagnoses (including a healthy screening result) were included (Figure 1), and >1 diagnosis per patient was possible. Final diagnoses were assigned by a clinician.

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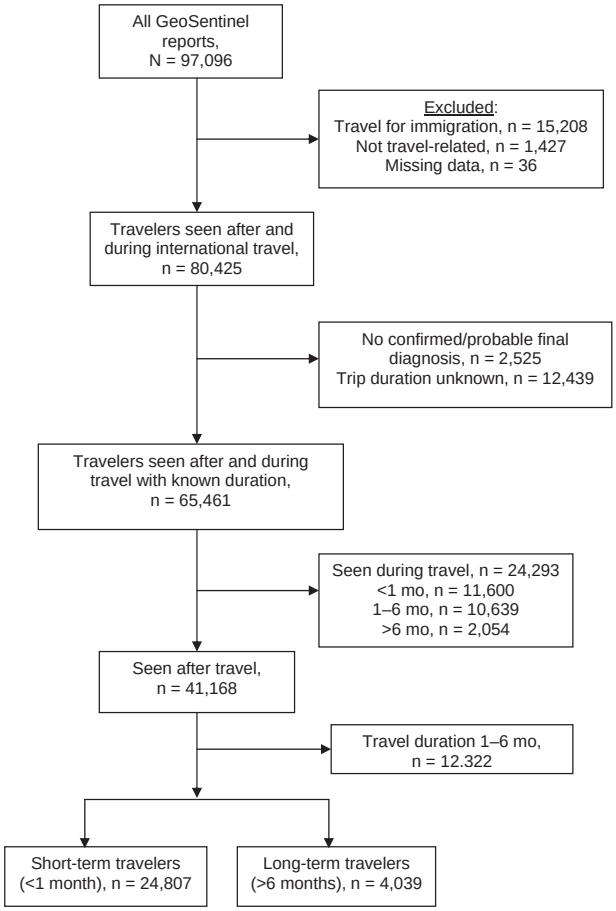

Figure 1. Flow chart for analysis of illness and injury in long-term travelers, GeoSentinel Surveillance Network, June 1996–December 2008.

Data were collected according to a standardized, anonymous questionnaire and entered into a Structured Query Language database. The questionnaire comprised demographic data (i.e., age, gender, country of birth, country of residence), travel history, inpatient or outpatient status, major diagnoses, pretravel encounter for travel health advice, reason for most recent travel, patient classification, and risk level qualifier (e.g., prearranged or organized travel, risk travel, and expatriate status). Included in the analysis were persons traveling for tourism, visits to friends and relatives (VFR), business, military purposes, education, research, or missionary/volunteer work. We excluded records lacking an exposure destination or duration of travel, as well as records of immigrating travelers, travelers with multiple trips without a specified location of exposure, final diagnoses attributed to travel of unspecified duration, travel duration of 1–6 months, and travelers seen during travel. We defined long-term travel as duration >6 months and short-term travel as duration <1 month. Data for specific diagnoses and syndromes were analyzed for travelers seen after travel.

Diagnostic Categories

Final diagnoses were assigned a diagnostic code from a standardized list of ≈500 diagnoses, which were categorized into 21 broad syndrome groups, as previously described (*10*). Diagnosis codes with clear causal routes were analyzed by the following categories: ingestion, vector-borne, contact (including respiratory, droplets, blood, body fluid, sexual transmission), environment (water, soil, animal contact), psychosocial, and medication intolerance.

Statistical Analysis

Data were analyzed by using SAS software, version 9 (SAS Institute, Cary, NC, USA). Proportionate illness was calculated as the number of patients with a specific or grouped diagnosis as a proportion of short-term or long-term travelers, expressed per 1,000 persons in that category (*10,11*). Statistical significance was determined by using χ^2 tests for categoric variables. For the most common diagnoses in long-term travelers, odds ratios (ORs) with 95% confidence intervals (CIs) were used to compare long-term with short-term travelers. A 2-sided significance level of $p<0.05$ was chosen. To avoid a regional bias (i.e., some exposure regions differed significantly between long-term and short-term travelers), we calculated ORs for the most common diagnoses in long-term travelers for the specific regions.

For long-term travelers, we performed multivariate logistic regressions to identify significant factors associated with various diseases. We adjusted for age, sex, pretravel encounters, reason for travel, and geographic region visited. Significant factors ($p<0.05$) were determined from stepwise selection.

Results

Demographics

Of 41,168 eligible persons seen after travel, 24,807 (60.3%) traveled for <1 month (short-term travelers), 12,322 (29.9%) traveled for 1–6 months, and 4,039 (9.8%) traveled for >6 months (long-term travelers). Mean ages were 33 years for long-term travelers and 38 for short-term travelers (online Appendix Table 1, available from www.cdc.gov/EID/content/15/11/1773-appT1.htm). The male: female ratio was 4:3. Most long-term travelers (90%) were 20–64 years of age, and most originated from countries in western Europe (43%) or North America (29%). Median duration for long-term travel was 365 days (mean 693 days, range 243–713 days) and for short-term travel was 14 days (mean 15 days, range 9–21 days).

Long-term travelers more often traveled for volunteer activities or research (40% vs. 7%) and business (25% vs. 14%) and less often for tourism (29% vs. 70%). A larger proportion of long-term than short-term travelers were male

(57% vs. 50%) and expatriates (54% vs. 9%), and most had sought pretravel medical advice (70% vs. 49%).

Long-term travelers more often traveled to sub-Saharan Africa (34%) and South America (16%) than did short-term travelers. Similar proportions of long- and short-term travelers went to south-central Asia (14% and 13%, respectively), and the proportion of long-term travelers with exposure in Southeast Asia was lower than that of short-term travelers. Intervals between return from travel to visit to a GeoSentinel site after long-term travel were <1 week (32%), 1–6 weeks (38%), and >6 weeks (30%).

Syndromes

Predominant syndromes in long-term travelers seen after travel were febrile systemic illness, acute diarrheal syndrome, dermatologic problems, and other gastrointestinal problems (online Appendix Table 2, available from www.cdc.gov/EID/content/15/11/1773-appT2.htm). A larger proportion of long-term than short-term travelers were determined to be healthy (196/1,000 travelers vs. 49/1,000 travelers).

Most Common Diagnoses and Proportionate Illness

Proportions of common diagnoses in long-term travelers by world region visited are shown in Figure 2. Long-term travelers were significantly more likely than short-term travelers to have chronic diarrhea (OR 1.20, 95% CI 1.04–1.38); giardiasis (OR 1.57, 95% CI 1.32–1.86); *P. falciparum* malaria (OR 1.50, 95% CI 1.26–1.78); irritable bowel syndrome (postinfectious) (OR 1.69, 95% CI 1.41–2.01), *P. vivax* malaria (OR 2.46, 95% CI 1.92–3.17); fatigue >1 month (OR 3.09, 95% CI 2.86–4.01); eosinophilia (OR 3.34, 95% CI 2.53–4.42); cutaneous leishmaniasis (OR 4.89, 95% CI 3.55–6.73); unspecified schistosomiasis (OR 4.45, 95% CI 3.16–6.25 [OR 4.26 for all schistosomiasis diagnoses together]); and *Entamoeba histolytica* diarrhea (OR 3.33, 95% CI 2.34–4.73) (Table 1). The most frequent regions of exposure for long-term versus short-term travelers were sub-Saharan Africa (34.26% vs. 24.59%; OR 1.60, 95% CI 1.48–1.73), followed by South America (16.38% vs. 7.30%; OR 2.49, 95% CI 2.24–2.76) and Southeast Asia (12.59% vs. 18.90%; OR 0.56, 95% CI 0.5–0.62, p = 0.00000) (online Appendix Table 1). Diagnoses of acute infections (such as dengue fever, rickettsiosis, acute diarrhea, acute bacterial diarrhea, influenza, and sexually transmitted infections), animal bites, and insect bites were significantly more common in short-term travelers.

Comparison of Diagnoses by Causal Route

Long-term travelers most commonly had diagnoses related to diseases with transmission by vectors or by ingestion. Larger proportions of long-term than short-term travelers had vector-borne diseases, contact-transmitted diseases (person-to-person, droplet, respiratory, sexually

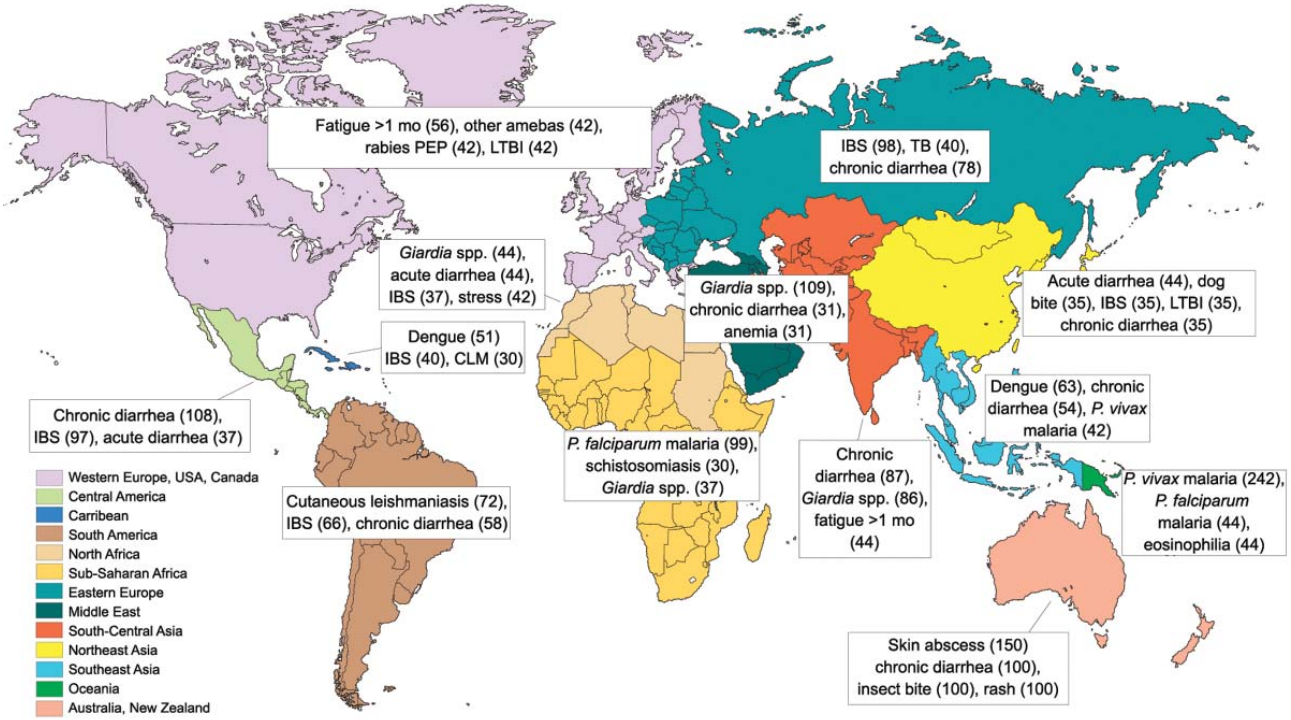

Figure 2. Proportionate illness (per 1,000 ill travelers) for the most frequent diagnoses in long-term travelers, by world geographic region visited, GeoSentinel Surveillance Network, June 1996–December 2008. PEP, postexposure prophylaxis; IBS, irritable bowel syndrome; TB, tuberculosis; LTBI, latent TB infection; CLM, cutaneous larva migrans; *P., Plasmodium*.

Table 1. Most common diagnoses for long-term travelers (n = 4,742) seen after travel and proportionate illness compared with short-term travelers (n = 28,618), GeoSentinel Surveillance Network, June 1996–December 2008*

Rank†	Diagnosis	Rate/1,000 travelers	Odds ratio (95% confidence interval)				
			Overall	South America	Southeast Asia	Sub-Saharan Africa	All other regions
1	Diarrhea, chronic unknown	50	1.20‡ (1.04–1.38)	1.19 (0.81–1.75)	1.59§ (1.05–2.39)	0.92 (0.64–1.31)	1.19 (0.99–1.44)
2	*Giardia* spp.	36	1.57‡ (1.32–1.86)	0.85 (0.49–1.47)	1.48 (0.80–2.73)	1.93‡ (1.39–2.67)	1.59‡ (1.26–2.01)
3	Irritable bowel syndrome, postinfectious	36	1.69‡ (1.41–2.01)	2.13§ (1.42–3.18)	2.76§ (1.52–5.02)	1.59¶ (1.03–2.45)	1.42§ (1.11–1.80)
4	Malaria, *Plasmodium falciparum*	36	1.50‡ (1.26–1.78)	NA	5.05‡ (2.58–9.88)	1.05 (0.86–1.27)	2.77§ (1.58–4.87)
6	Malaria, *P. vivax*	19	2.46‡ (1.92–3.17)	0.83 (0.33–2.07)	4.79‡ (2.86–8.01)	1.14 (0.67–1.94)	3.66‡ (2.57–5.22)
8	Fatigue >1 month (not febrile)	18	3.09‡ (2.86–4.01)	3.45§ (1.59–7.50)	1.94 (0.86–4.37)	1.79 (0.98–3.25)	4.27‡ (3.01–6.05)
9	Eosinophilia	17	3.34‡ (2.53–4.42)	3.49§ (1.56–7.83)	3.11§ (1.46–6.60)	4.11‡ (2.46–6.84)	2.89‡ (1.91–4.37)
11	Leishmaniasis, cutaneous	14	4.89‡ (3.55–6.73)	9.14‡ (5.15–16.24)	NA	0.77 (0.09–6.40)	2.30§ (1.35–3.92)
12	Schistosomiasis, human species unknown#	13	4.45‡ (3.16–6.25)	2.92 (0.18–46.68)	3.30 (0.34–31.80)	3.10‡ (2.09–4.59)	7.44‡ (3.83–14.47)
17	TB, positive PPD or IGRA	11	3.26‡ (2.33–4.56)	2.92 (0.73–11.72)	24.27‡ (8.52–69.17)	2.44¶ (1.13–5.26)	2.68‡ (1.71–4.18)
18	*Entamoeba histolytica*, diarrhea	11	3.33‡ (2.34–4.73)	2.57 (0.93–7.10)	1.52 (0.34–6.77)	3.88‡ (1.95–7.72)	3.52‡ (2.23–5.56)
21	Stress	9	5.70‡ (3.77–8.61)	NA	1.65 (0.20–13.73)	7.57‡ (3.13–18.30)	5.55‡ (3.32–9.30)
22	Epstein-Barr virus	8	2.60‡ (1.72–3.91)	12.86‡ (3.65–45.27)	2.99¶ (1.20–7.48)	0.38 (0.05–2.96)	2.29§ (1.30–4.03)
25	Strongyloidiasis, simple intestinal	7	1.85§ (1.24–2.75)	0.83 (0.17–4.01)	3.11¶ (1.14–8.53)	1.62 (0.88–2.99)	1.89 (0.94–3.81)

*Long-term travel is defined as >6 mo, short-term travel as <1 mo. NA, not applicable; TB, tuberculosis; PPD, purified protein derivative test; IGRA, interferon-gamma release assay.
†Among 25 most common illnesses for all travelers.
‡p<0.0001.
§p<0.01.
¶p<0.05.
#Aggregated schistosomiasis diagnoses (mansoni, haematobium, japonicum, mekongi, and unknown) are grouped together and shown in online Appendix Table 3, available from www.cdc.gov/EID/content/15/11/1773-appT.htm.

transmitted), and psychological problems (Table 2). Diagnoses for long-term travelers varied for travel and region of exposure (online Appendix Table 2).

Discussion

Existing data are limited regarding the number and proportion of all long-term travelers. This analysis of the GeoSentinel Surveillance Network found that long-term travelers constituted 9.8% of all travelers visiting GeoSentinel sites. In comparison, 5 travel medicine clinics in the Boston area found that ≈5% of travelers planned trips of ≥4 months' duration (*12*). More than 66% of long-term travelers seen in the GeoSentinel Network had pretravel encounters, a higher percentage than shown in airport surveys of all travelers (range 31%–52% [*13–15*]). Many organizations, such as missions, corporations, and aid agencies, require health screening of their employees or participants after long-term overseas service, which may have resulted in the high yield of healthy diagnoses (196/1,000 travelers). Particular areas to consider for pretravel counsel for long-term travelers are vector-borne and contact-transmitted diseases and psychological problems.

Ingestion Transmission

In our analysis, ingestion was the most common attributable route of transmission for diseases in long-term travelers, although long-term travelers sought treatment less frequently than short-term travelers for ingestion-transmitted diseases (OR 0.81, p<.0001). Enteric fever, acute diarrhea, chronic diarrhea, giardiasis, and other gastrointestinal parasites were reported significantly more often in long-term than short-term travelers (p = 0.0024 for enteric fever, p<0.0001 for the rest). Young age was associated with giardiasis and other gastrointestinal parasites, possibly because of inexperience or more risk-taking behavior. Giardiasis occured more often in long-term travelers to sub-

Saharan Africa than in short-term travelers there (OR 1.93, p<.0001); that difference was not apparent for travelers to South America and Southeast Asia.

Epidemiologic surveillance of PCVs (1985–1987, >5,500 volunteers) found similar results: among the most common illnesses during service were diarrhea and giardiasis (*16*). More recently, the major health problems experienced by PCVs in Madagascar were gastrointestinal, dermatologic, and respiratory (*5*). Examination during home leave of British missionaries who served in 27 countries found diarrhea and giardiasis to be the most common problems, and those who served in West Africa had more illnesses (*7*). Not surprisingly, children of missionaries encountered poor water treatment and food sanitation (*2*); before hepatitis A vaccine was available, a questionnaire of mission boards identified viral hepatitis as the most serious health problem among missionaries (*4*). Among 328 North American missionaries evaluated during 1967–1984, 5.8% seroconverted to hepatitis A (this percentage may underestimate risk without prophylaxis because they presumably had received immune globulin); 0% seroconverted to hepatitis E after an average of 7.3 years of service (*17*). We found a higher risk for hepatitis A in long-term travelers, but the difference was not statistically significant (OR 1.21, p = 0.5328). With the wide availability of hepatitis A vaccine today and the consensus for its broad use for travel to developing regions, most travelers, especially those planning long-term travel, are expected to have been vaccinated.

A major vaccine-preventable disease is typhoid fever. Long-term travelers more frequently had enteric fever (typhoid and paratyphoid) than did short-term travelers (9/1,000 vs. 5/1,000 travelers; OR 1.70, p = 0.0024). A past estimate of the attack rate for typhoid in expatriates was 3/100,000 travelers per month of stay (*18*). Enteric fever was significantly associated with travel to south-central Asia, reflecting the distribution of enteric fever; vaccination should particularly be emphasized to long-term travelers, even though the efficacy of currently available vaccines is only 60%–70%.

A survey of corporate expatriates found that food safety practices worsened as duration of stay increased (*3*). Adherence to food and water precautions is difficult to maintain, as noted in a survey of 140 travelers in India whose median trip duration was 5 months (*19*). None had adhered fully to food and water precautions; 83% had diarrhea, and 60% had diarrhea for ≈3% of their journey time.

Vector Transmission

Long-term travelers more frequently had vector-borne diseases than did short-term travelers because of the longer period during which bites can occur and possibly less vigilance about personal protection measures and/or chemoprophylaxis during long stays. Long-term travelers also may have more primitive, remote, and rural living conditions than short-term travelers. Leishmaniasis, malaria, and filariasis were all reported more frequently in long-term travelers than in short-term travelers (14, 68, and 5/1,000 vs. 3, 39, and 2/1,000, respectively; p<0.0001). Regional variations were consistent with geographic disease distribution (Table 1; online Appendix Table 3, available from www.cdc.gov/EID/content/15/11/1773-appT3.htm). Other associations of long-term travel and illness were male gender (leishmaniasis, malaria), VFR (malaria, filariasis), and missionary/volunteer/aid work/research (filariasis). Posttravel medical evaluation of 212 British missionaries indicated malaria as among the most common overseas illnesses (87.3/1,000 person-years at risk); more illnesses were associated with west Africa (688/1,000 person years at risk) than other regions (*7*). Among PCVs in Madagascar, 11 (15.9%) had malaria (8 cases/100 PCV-years) (*5*). Children of missionaries received suboptimal malaria prophylaxis (*2*). Business travelers, despite understanding their risk for malaria, failed to use appropriate personal protection when duration of travel increased (*20*). Corporate expatriates also adhered poorly to malaria chemoprophylaxis with longer stays in risk areas (*3*). Long-term travelers need better preparation for preventing, diagnosing, and treating malaria; novel approaches such as provision of rapid malaria tests and adequate self-treatment medication should be considered for this high-risk population. Widespread proliferation of counterfeit drugs requires long-term travelers to take adequate supplies with them (*21*,*22*).

Seroprevalence studies confirm exposures to dengue virus in regions to which it is endemic: a serosurvey of 323 development workers and family members had increased seropositivity with longer stay (*23*). Seroconversion occurred in 6.7% of 104 Israeli travelers with trips ≥3 months' duration in dengue-endemic countries and 2.9% of 477 Dutch travelers to Asia (≈30/1,000 person-months of stay) (*24*,*25*). We found dengue was diagnosed less commonly in long-term travelers (OR 0.69, p = 0.0022) than in short-term travelers, perhaps because dengue has a short incubation period and many infections occurring during prolonged stays are not confirmed; diagnostic tests are usually not performed in countries endemic for dengue because of expense or lack of diagnostic capabilities.

Psychological Diagnoses

Some psychological diagnoses were reported significantly more often in long-term travelers (OR 2.80, p<0.0001), particularly depression (OR 3.03, p<0.0001), nonmefloquine psychosis (OR 3.89, p = 0.0006), stress (OR 5.70, p<0.0001), and fatigue (OR 3.09, p<0.0001); rates of anxiety, insomnia, substance abuse, and posttraumatic stress disorder were equivalent to or lower than rates in short-term travelers. The increased number of

missionary/volunteer/research/aid workers with stress was most significant (OR 32.18, (p<0.0001). Psychological rates were highest in eastern Europe and northern Africa and lowest in the Caribbean and Southeast Asia. Mission boards consider psychological conditions to be among the most common and serious conditions, specifically depression, stress, and burnout (*4*). Furthermore, psychiatric illness caused 60% of premature repatriations among British missionaries or their family members serving overseas (*7*). Nine (14%) of 66 fatalities among PCVs from 1984 to 2003 were caused by mental illness (*26*).

In a survey of 1,340 long-term travelers from Israel (mean stay 5.3 months), 151 (11.3%) had neuropsychiatric problems during travel with a higher proportion of women (54.6%) and an association with mefloquine use (*27*). Further assessment found a mean stay abroad of 5.3 months. However, data on PCVs found that mefloquine adverse events usually occurred early in prophylaxis (*28*).

Table 2. Comparison of rates for diagnoses among long-term and short-term travelers seen after travel by causal routes and preventive measures, GeoSentinel Surveillance Network, June 1996–December 2008*†

Grouped diagnoses	Rate/1,000 travelers		Odds ratio (95% CI)
	Short-term travelers	Long-term travelers	
Vector-borne infections	76	109	1.47 (1.33–1.63)
Dengue	24	17	0.69 (0.551–0.88)
Chikungunya	2	2	1.16 (0.59–2.29)
Leishmaniasis	3	14	4.89 (3.55–6.73)
Malaria, all species	39	68	1.83 (1.61–2.08)
Rickettsiosis	8	2	0.22 (0.11–0.45)
Filariasis	2	5	3.22 (1.981–5.24)
Ingestion	257	219	0.81 (0.75–0.87)
Enteric fever	5	9	1.70 (1.20–2.41)
Hepatitis A	2	3	1.21 (0.67–2.19)
Diarrhea, acute	123	41	0.31 (0.27–0.36)
Diarrhea, chronic	45	54	1.20 (1.04–1.38)
GI bacteria	34	15	0.42 (0.33–0.53)
Giardiasis	24	36	1.57 (1.32–1.86)
GI parasites	55	108	2.08 (1.88–2.312)
Contact‡	33	38	1.15 (0.70–1.90)
Influenza	8	5	0.60 (0.39–0.92)
Latent TB (positive PPD or IGRAs)	4	11	3.26 (2.33–4.56)
Acute mononucleosis syndrome (CMV, EBV, other)	7	11	1.60 (1.18–2.18)
Hepatitis B	2	2	0.67 (0.31–1.47)
Hepatitis C	1	2	1.73 (0.85–3.49)
Other sexually transmitted infections	7	4	0.67 (0.43–1.05)
HIV (acute infection)	2	1	0.39 (0.12–1.27)
Environment	119	87	0.71 (0.63–0.79)
Schistosomiasis	6	24	4.26 (3.35–5.42)
Strongyloides	4	7	1.85 (1.24–2.75)
Hookworm	2	2	1.26 (0.62–2.60)
Animal bite	44	13	0.28 (0.22–0.37)
Other skin contact, noninfectious	60	18	0.29 (0.23–0.36)
Fungal infection (superficial/cutaneous mycosis)	4	10	2.33 (1.66–3.28)
Rash	19	19	0.98 (0.78–1.23)
Psychological	15	40	2.80 (2.35–3.33)
Anxiety	3	4	1.60 (0.96–2.65)
Depression	2	6	3.03 (1.89–4.86)
Psychosis, nonmefloquine	1	2	3.89 (1.68–8.99)
Stress	2	9	5.70 (3.77–8.61)
Fatigue >1 mo	6	18	3.09 (2.86–4.01)
Adverse events from medication or vaccine	7	3	0.44 (0.26–0.74)
Mefloquine intolerance	4	1	0.19 (0.07–0.52)
Medication intolerance, nonmefloquine	3	2	0.83 (0.44–1.56)

*Long-term travel defined as >6 mo, short-term as <1 mo. CI, confidence interval; GI, gastrointestinal; TB, tuberculosis; PPD, purified protein derivative; IGRA, interferon-gamma release assay; CMV, cytomegalovirus; EBV, Epstein-Barr virus.
†Diagnoses with proportionate illness <1/1,000 are omitted from table listing, such as hepatitis E, hepatitis delta, meningococcal meningitis, *Haemophilus influenzae* type b, pneumonia, pneumococcal pneumonia, varicella, chronic hepatitis, leptospirosis, altitude sickness, posttraumatic stress disorder, substance abuse, insomnia, delusional parasitosis, trauma, and violence exposure. Some patients may have >1 diagnosis.
‡Includes respiratory illnesses, blood/body fluid exchange, and sexually transmitted infections.

Although our analysis identified no substance abuse, an earlier study of 18–30-year-old travelers to the tropics found that approximately one third of survey responders used illicit drugs during their trip, especially travelers to the Far East. The strongest predictors of drug abuse were the combination of female sex and travel to Asia, education ≤12 school years, age ≤25 years, and lack of malaria prophylaxis. Providing antidrug brochures did not affect the drug abuse rate (*29*).

Contact or Person-to-Person Transmission

Latent tuberculosis (positive purified protein derivative [PPD] or interferon-gamma release assays) was diagnosed more commonly in long-term than in short-term travelers (11 vs. 4/1,000; OR 3.26, p<0.0001), whereas influenza was diagnosed less commonly in long-term travelers (5 vs. 8/1,000, OR 0.60, p = 0.0183). PCVs serving in Madagascar most commonly reported respiratory problems and gastrointestinal and skin conditions, including 5.8% with Mantoux of ≥5 mm induration (3 cases/100 volunteer-years) (*5*). Peace Corps data from January 1, 1996, through December 31, 2005, showed rates of positive PPD conversions and active TB cases to be 1.283 and 0.057 per 1,000 volunteer-months, respectively; the African region had the highest PPD conversion rate, followed by the European region (*30*). Other studies on PPD conversion among travelers have reported rates up to 3.5/1,000 person-months (*31*).

Acute mononucleosis syndromes was significantly higher in long-term than in short-term travelers (11 vs. 7/1,000 travelers, OR 1.60, p = 0.0024) but no significant difference for other diseases transmitted through sex or body fluids. Younger age, male sex, lack of pretravel advice, and exposure in western Europe were associated with diagnoses of acute mononucleosis syndromes.

Among PCVs in Madagascar, the reported incidence of sexually transmitted infections was 6.9% (5.6% of females and 13.3% of males); 8.7% of those volunteers needed postexposure prophylaxis for human immunodeficiency virus (*5*). Long-term missionaries in developing countries had seroconversion rates of 5.5% to antibody to hepatitis B core antigen and 0.6% to antibody to hepatitis C virus, suggesting significant exposure to hepatitis B (*17*). In our study, hepatitis B infection was diagnosed more often in short-term than long-term travelers, although not significantly so (OR 0.67, p = 0.3131). More potential exposures to hepatitis B is expected during long-term travel; therefore, hepatitis B vaccine is routinely recommended for long-term travelers. (*32*). A plausible explanation for our result is that a high percentage of long-term travelers had been vaccinated against hepatitis B. Hepatitis B infection, a vaccine-preventable disease, should be targeted for prevention in travelers.

Environmental Cause

Among diagnoses attributed to soil and water exposure, schistosomiasis and strongyloidiasis were more common in long-term travelers (24 and 7/1,000 travelers; OR 4.26, p<0.0001, and 1.85, p = 0.0021, respectively) and were associated with males. Schistosomiasis was also associated with tourism and missionary/volunteer/research/aid work, and strongyloidiasis was associated with VFR. An earlier study found that 8 (11.6%) of 69 PCVs who served in Madagascar had antischistosomal antibodies (*5*).

Although ectoparasites (scabies, sand flea, and head lice) were reported in 11.6% of PCVs (*5*), long-term travelers in our study, compared with short-term travelers, had a proportionately lower number of other skin conditions with possible environmental exposures (OR 0.29, p<0.0001) but a proportionately higher number of fungal skin infections (OR 2.33, p<0.0001).

Rabies risk has been considered to increase with longer duration of travel, and preexposure prophylaxis is typically recommended, particularly for long stays. Our data showed a lower proportionate need for postexposure prophylaxis (not actual rabies) in long-term travelers than in short-term travelers (7 vs. 23/1,000, OR 0.31, p<0.0001), possibly because long-term travelers may be more knowledgeable or better educated about animal exposure risks, more likely to avoid exposures, and more likely to have been vaccinated before travel. In PCVs, potential exposure to rabies was 10× higher abroad than domestically (*1*). Among Norwegian missionaries serving in developing countries for 4–5 years, 7% had possible rabies exposure (*33*). A study of travelers returning from travel >1 month identified 1.6% injured by a potentially rabid animal (mainly dog and monkey), or 2.66 per 1,000 travelers per month (*34*). Those injured had significantly longer trips (mean 6.9 mo, ±3.8 SD); only 31% sought appropriate medical treatment (*34*).

Injury

Mission boards consider injury among the most common and serious conditions (*4*,*35*). The leading cause of death in Africa for American missionaries during 1970–1985 was motor vehicle injury (*35*). Of 66 deaths occurring in PCVs from 1984 to 2003, injury was the primary cause (45), including motor vehicle injuries, most commonly by automobile but also by bus, truck, taxi, minibus taxi, and motorcycle (*26*). Among 1,190 returned expatriates, most of whom had served the International Committee of the Red Cross for ≥6 months, 10% reported injury or accident during their service (*36*). Injured travelers are unlikely to seek care at a GeoSentinel site, so our analysis has limited data about injury.

Limitations

Our findings are subject to several limitations. The GeoSentinel database captures travelers who sought treatment at specialized travel and tropical medicine clinics and who may not be representative of all travelers. Long-term travelers may be more likely than short-term travelers to seek a GeoSentinel site because of concern about unusual tropical diseases. We used only GeoSentinel data, so proportionate frequency of diagnoses for long-term travelers compared with short-term travelers in this database can be derived, but not risk for illness. Missing travel duration eliminated ≈10% of records from analysis. Paucity of injury data is another limitation of the analysis because injury is a major cause of illness and death in long-term travelers. Similarly, travelers with dental, ophthalmologic, obstetric, and gynecologic problems rarely visit GeoSentinel sites.

Conclusions

Approximately 10% of all ill travelers seen at GeoSentinel sites are long-term travelers. Long-term travelers are characterized by male gender and travel for missionary/volunteer/research or business; most had pretravel evaluations. Among the problems more frequently seen in long-term travelers than in short-term travelers are infections with long incubation and long-lasting or chronic durations; malaria is especially important, as are leishmaniasis, filariasis, gastrointestinal parasites, schistosomiasis, and latent tuberculosis. Many vector-borne diseases with short incubation periods (e.g., dengue, chikungunya, rickettsia) are diagnosed more often in short-term travelers. These findings do not mean that these infections occur less often in long-term travelers, only that they are not active when long-term travelers are seen after travel; a similar situation may be true for animal bites. Many common infections seen in long-term travelers are preventable by vaccines, vector avoidance, food/water precautions, and avoidance of soil and fresh water. Psychological problems, especially depression, stress, nonmefloquine psychosis, and prolonged fatigue, increase with long-term travel. The high OR (32.18) of missionary/volunteer/research/aid workers with stress merits attention and intervention. Clinicians must be alert to psychological problems and manage them, as reentry and readjustment for long-term travelers may be difficult. Among the vaccine-preventable diseases, enteric fever and hepatitis A increase with long-term travel. Because >50% of ailments for which long-term travelers visit a healthcare provider are preventable and 70% of long-term travelers had pretravel visits, opportunities exist to educate, vaccinate, provide malaria chemoprophylaxis, and prepare these travelers for possible break-through infection.

Disease patterns differed significantly for long-term and short-term travelers. Particular areas of concern for long-term travelers are vector-borne, ingestion-transmitted, contact-transmitted disease, and psychological problems. Our results can help identify priorities for screening and diagnosing illnesses in long-term travelers and for providing evidence-based pretravel advice.

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Multicenter EuroTravNet/ GeoSentinel Study of Travel-related Infectious Diseases in Europe

Philippe Gautret, Patricia Schlagenhauf, Jean Gaudart, Francesco Castelli, Philippe Brouqui, Frank von Sonnenburg, Louis Loutan, and Philippe Parola, for the GeoSentinel Surveillance Network[1,2]

We analyzed prospective data on 17,228 European patients who sought treatment at GeoSentinel sites from 1997 to 2007. Gastrointestinal illness (particularly in tourists), fever (those visiting friends and relatives [VFRs]), and skin disorders (in tourists) were the most common reasons for seeking medical care. Diagnoses varied by country of origin, region visited, or categories of travelers. VFRs who returned from sub-Saharan Africa and Indian Ocean islands were more likely to experience falciparum malaria than any other group. Multiple correspondence analysis identified Italian, French, and Swiss VFRs and expatriate travelers to sub-Saharan Africa and Indian Ocean Islands as most likely to exhibit febrile illnesses. German tourists to Southeast and south-central Asia were most likely to seek treatment for acute diarrhea. Non-European travelers (12,663 patients from other industrialized countries) were less likely to acquire certain travel-associated infectious diseases. These results should be considered in the practice of travel medicine and development of health recommendations for European travelers.

In recent years, growth in international travel has been ≈6% per year, and similar trends are expected in the future (*1*). This growth has been strongly driven by travelers to newly popular destinations in Asia and the Pacific, Africa, and the Middle East (*1*). Approximately 80 million persons from industrialized nations travel to the developing world each year, and an estimated >200 million persons now reside outside their country of birth (*1*).

European travelers represent most of the international travelers, with Germany, United Kingdom, France, and Italy the leading countries of origin (*2*). With few exceptions, no European consensus exists on recommendations for travelers about risk assessment, malaria prophylaxis, or vaccinations. International references include the World Health Organization green book (*3*), which emphasizes risk assessment by rates of diseases in local populations; and the Centers for Disease Control and Prevention yellow book (*4*), which examines risk in the context of American travelers. Yet, whether these guidelines are appropriate in the European context is not known.

The intense international traffic between Europe and the rest of the world means that travelers have become a key element in the global spread of infectious diseases. These diseases may be introduced into domestic European populations and environments that are receptive to further spread. In 2003, severe acute respiratory syndrome (SARS) was introduced to France by 1 patient who returned from Vietnam (*5*). Malaria has recently reemerged in Italy and in France (Corsica), resulting from local transmission by anopheline mosquitoes that fed on travelers who had become infected with *Plasmodium vivax* during travel (*6*). More recently, chikungunya virus (CHIKV) appeared as

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[1]A list of GeoSentinel Surveillance Network members who also contributed data is given at the end of this article.

[2]The GeoSentinel sites in Europe have recently grouped together within GeoSentinel to form the core sites of EuroTravNet (www.eurotravnet.eu), the European Centre for Disease Prevention and Control corresponding network for tropical and travel medicine.

a paradigm of an infectious disease that rapidly became global as highly viremic travelers acted as efficient carriers of the virus (*7*). After CHIKV-infected persons in eastern Africa, Indian Ocean islands, India, and Southeast Asia, a new CHIKV variant reached Europe and affected local populations in Italy through 1 infected traveler (the index case-patient) and transmission by indigenous European mosquito vectors (*8*). In April 2009, an influenza A pandemic (H1N1) 2009 virus emerged in humans in North America and reached Europe soon after through returned travelers (*9*).

European physicians should be prepared to encounter and recognize infectious imported diseases. Facing the symptoms and syndromes in the ill returned traveler requires an understanding of the common etiologic agents encountered by different populations of travelers (*10*). Accurate epidemiologic data are needed about travel-associated infectious diseases in travelers returning to European countries. Some data on diseases among Europeans who traveled to developing countries recently have been published but were limited to 1 country of origin (*11–13*), a short period of study, specific diseases (*14–16*), a specific destination (*17*), or a certain type of traveler (*18*). A comprehensive multicenter comparison of the spectrum of illnesses among European travelers, including a broad sample of destinations, has been missing. Our objective in this study was to determine the epidemiology of travel-related infectious diseases in a large set of ill returned European travelers over a substantial period and to compare this with the epidemiology of disease in travelers from other industrialized countries outside Europe.

Patients and Methods

Data Source

The GeoSentinel Surveillance Network consists of specialized travel/tropical medicine clinics on 6 continents where ill travelers are seen during or after traveling to a wide range of countries and where information about travelers is prospectively recorded (*19*) in a standardized format. To be eligible for inclusion in the GeoSentinel database, patients must have crossed an international border and have received medical attention at a GeoSentinel clinic for a presumed travel-related illness. We included western European patients who sought treatment at GeoSentinel sites after travel from March 1997 through November 2007. Persons were placed in 3 different categories: classic traveler, immigrant traveler, and expatriate traveler (Table 1). Reasons for travel were classified as the following: tourism, business, research/education, missionary/volunteer work, or visiting friends and relatives (VFRs). Individual countries visited were grouped into 12 regions (*19*). Medical data included the final physician-assigned diagnosis, according to a standardized list of 556 possible individual diagnoses of infectious diseases that were also categorized under 21 broad syndromes as previously described (*19*). European patients were compared with all other ill non-European returned patients on the basis of information obtained from GeoSentinel sites in the United States, Canada, Australia, and New Zealand.

Statistical Analysis

Data were entered and managed in Microsoft Access (Microsoft Corp., Redmond, WA, USA). In our evaluation, proportionate morbidity refers to the number of cases of a specific diagnosis (or of a group of specific diagnosis within a syndrome group) compared with all cases of ill returned travelers seen at GeoSentinel clinics during the same period. Differences in proportions (qualitative variables) were tested by using Pearson χ^2 or Fisher exact tests. Analysis of variance or Kruskal-Wallis tests were used for quantitative variables. Because of the large numbers of statistical tests performed, a p value ≤ 0.001 was considered significant.

Diagnosis, exposure regions, residence region, and travel types were analyzed by using multiple correspondence analysis (MCA) (*20–22*). MCA was performed by using the ANADEV freeware (www.lertim.org), developed by the Laboratory of Biomathematics, Faculty of Medicine of Marseille. Odds ratios (ORs) (European vs. non-European) by diagnosis were estimated by using logistic regression and adjusted for travel duration. All statistical tests were 2-sided. Percentages and odds ratios (with 95% confidence intervals), comparisons, and graphic analysis were carried out by using the R 2.8.1 environment (www.r-project.org).

Table 1. Categories of ill European* returned travelers seen at GeoSentinel sites, 1997–2007

Category	Definition
Classic traveler	European country–born person living in Europe who traveled to a developing country and has returned to his or her home country.
Immigrant traveler	Person born in a developing country who at some time has emigrated to Europe,† including refugees, where a permanent residence has been established, and who later travels to a developing country and returns to Europe.
Expatriate traveler	European-born person who grew up in Europe and whose current country of residence is a developing country. They were included when they sought treatment at a GeoSentinel site after they returned to Europe and/or after travel while still expatriating.

*From Western Europe (*19*).
†Patients whose purpose of travel was the initial immigration travel from their birth country to Europe were excluded.

Results

Demographic and Travel Data

A total of 17,228 European patients were included: 13,913 (80.8%) classic travelers, 2,415 (14.0%) immigrant travelers, and 900 (5.2%) expatriate travelers (Figure 1). Demographic and travel data are presented in Table 2. Most patients were seen as outpatients who sought treatment at the clinics <2 weeks post travel. Immigrant travelers sought markedly less pretravel advice and were more likely to be inpatients than other groups; differences were significant (p<0.0001). Furthermore, European patients' main destination was Africa, followed by Asia; the proportion of patients returning from sub-Saharan Africa, Indian Ocean islands, and south-central Asia was higher in sites in Italy, France, and the United Kingdom, respectively (Figure 2). Non-Europeans (12,663 patients) had a lower proportion of immigrant travelers in the inpatient category, and non-European expatriates were younger, had a longer duration of travel, and sought pretravel advice more often (p<0.0001).

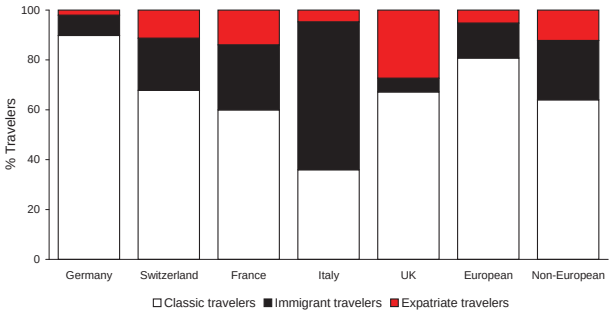

Figure 1. Proportion (%) of different categories of returned patients among 17,228 patients seen in GeoSentinel sites in Europe,* compared with 12,663 non-European patients sampled from the GeoSentinel database (1997–2007). *This proportion includes 11,848 from Germany, 2,818 from Switzerland, 971 from Italy, 931 from France, 289 from the United Kingdom, and 371 from other European countries.

Final Etiologic Diagnosis

The proportionate morbidity of some broad syndromes or etiologic diagnoses was higher in patients travelling to specific regions. This was obvious for acute diarrhea in North Africa, south-central Asia, and the Middle East, and etiologic diagnosis such as *Campylobacter* spp. in south-central and Southeast Asia, *Shigella* spp. in North Africa and south-central Asia, *Giardia* spp. in south-central Asia and South America and amebas in south-central Asia. Febrile systemic illnesses were more frequently reported from Indian Ocean islands, sub-Saharan Africa, and Oceania. *P. falciparum* malaria was more frequently observed in travelers returning from Indian Ocean islands and sub-Saharan Africa, *P. vivax* malaria in travelers from Oceania, Indian Ocean islands, and South America, and *P. ovale* and *P. malariae* malaria in travellers from Indian Ocean islands and sub-Saharan Africa. Dengue was more frequently reported from Southeast Asia, chikungunya from Indian Ocean Islands, and rickettsioses from sub-Saharan Africa, and salmonellosis from south-central Asia. Proportionate morbidity for dermatologic conditions was higher in Oceania, Southeast Asia, Central America, South America, and the Caribbean, including animal-related injuries requiring rabies postexposure prophylaxis (PEP) in North Africa, the Middle East, and Southeast Asia; larva migrans in Southeast Asia, the Caribbean, South America, and Central America; leishmaniasis in Central America and South America; and myasis in Central America. Finally, respiratory syndromes were more frequently reported in travelers returning from eastern Europe and northeastern Asia; genitourinary and sexually transmitted diseases (STDs) were more frequent in travelers from eastern Europe, Southeast Asia, and the Caribbean; schistosomiasis was more frequent in travellers from Africa and cerebromeningeal infections were more frequent in travelers from eastern Europe and North-Africa) (p<0.0001) (online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1783-Techapp.pdf).

Also, the proportionate morbidity of some broad syndromes or etiologic diagnoses was higher in persons returning to specific European countries, as illustrated for falciparum malaria (Italy, France), dengue (United Kingdom), CHIKV infection (France), animal-related injuries requiring rabies PEP (France, United Kingdom) and cerebromeningeal infections (Italy) (p<0.0001). The proportionate morbidity was also higher in some categories of traveler, such as diarrhea and dermatologic diseases (in classic tourist travelers), falciparum malaria and genitourinary infections and STDs (immigrant travelers who were VFRs), and *P. vivax* malaria (missionary/expatriate travelers) (p<0.0001). (For details, see online Technical Appendix.)

MCA highlights the possibility of diagnosis in certain groups and shows an association between German patients, who are classic travelers (traveling for tourism to Southeast and south-central Asia) and a diagnosis of acute diarrhea. The MCA also showed that French, Swiss, or Italian patients who are classified as immigrant or expatriate travelers (VFRs or travelers for missionary purposes to Africa or Indian Ocean islands) are most likely to seek treatment for febrile illness (online Technical Appendix).

Compared with the corresponding proportion of disease in non-European travelers, European classic tourist travelers had a lower proportionate morbidity (adjusted for travel duration) for certain diagnoses, such as schistosomiasis, cutaneous larva migrans, and animal-related injuries requiring rabies PEP, and a higher proportionate morbidity for genitourinary infections, STDs, and respira-

Table 2. Demographic and travel data for 17,228 European travelers seen at GeoSentinel European sites, compared with non-European travelers, 1997–2007*

Characteristic	European			Non-European†		
	Classic travelers	Immigrant travelers	Expatriate travelers	Classic travelers	Immigrant travelers	Expatriate travelers
Sex						
M	6,882 (49.5)	1,440.(59.6)	526 (58.4)	3,608 (44.5)	1,513 (50.2)	1,006 (64.9)
F	7,006 (50.4)	971 (40.2)	372 (41.3)	4,278 (52.8)	1,463 (48.6)	532 (34.3)
Unknown	25 (0.2)	4 (0.2)	2 (0.2)	215 (2.7)	37 (1.2)	11 (0.7
Median age, y (range)	34 (0–96)	36 (0–95)	37 (1–179)	32 (0–95)	40 (2–89)	23 (1–77)
Patient type						
Inpatient	611 (4.4)	887 (36.7)	65 (7.2)	436 (5.4)	323 (10.7)	53 (3.4)
Outpatient	13,243 (95.2)	1,507 (62.4)	785 (87.2)	7,233 (89.3)	2,595 (86.1)	1,448 (93.4)
Unknown	59 (0.4	21 (0.9	50 (5.6)	432 (5.3)	95 (3.2)	48 (3.1)
Median travel duration,‡ d (range)	21 (1–;212)	30 (1–180)	180 (1–1,555)	20 (1–212)	26 (1–198)	334 (1–1,010)
Pretravel advice						
Yes	8,212 (59.0)	525 (21.7)	518 (57.6)	4,169 (51.5)	647 (21.5)	1,209 (78.1)
No	3,252 (23.4)	1,206 (49.9)	186 (20.7)	2,678 (33.1)	1,927 (64.0)	216 (13.9)
Unknown	2,449 (17.6)	684 (28.3)	196 (21.8	1,254 (15.5	439 (14.6)	124 (8.0)
Reason for travel						
Tourism	11,200 (80.5)	525 (21.7)	124 (13.8)	5,317 (65.6)	813 (27.0)	81 (5.2)
Business	1,733 (12.5)	142 (5.9)	344 (38.2)	1,084 (13.4)	216 (7.2)	273 (17.6)
Missionary or volunteer work	775 (5.6)	59 (2.4)	422 (46.9)	1,225 (15.1)	137 (4.5)	1,190 (76.8)
Student	82 (0.6)	23 (1.0)	2 (0.2)	355 (4.4)	92 (3.1)	–
Healthcare seeking	8 (0.1)	–	–	–	1 (0.1)	–
Visiting friends or relatives	100 (0.7)	1,662 (68.8)	8 (0.9)	96 (1.2)	1,752 (58.1)	5 (0.3)
Military	15 (0.1)	4 (0.2)	124 (13.8)	24 (0.3)	2 (0.1)	–
Median time between travel end and presentation, d (range)	13 (1–156)	13 (1–139)	10 (1–153)	17 (1–154)	26 (1–157)	23 (1–165)

*All values are no. (%) except as indicated. For each demographic and travel variable, univariate global analyses were used for comparing means (analysis of variance) or percentages (χ^2 test). For example, age means (for each category) have been compared using an analysis of variance; percentages of men (for each category) have been compared by χ^2 test. All tests have shown significant results ($p<0.0001$).
†Data for 12,663 non-European patients sampled from the GeoSentinel database.
‡Travel duration and interval time were estimated using accurate data, available for 15,969 (92.7%) Europeans and 9,828 (77.6%) non-Europeans exhibiting a travel-associated disease along with a recent trip (<6 mo ago).

tory diseases when traveling to specific regions (Figure 3). Also, the *P. falciparum* malaria proportionate morbidity in immigrant travelers (VRFs) after travel to Africa or the Indian Ocean islands was higher in Europeans compared with non-Europeans (Figure 3).

Discussion

Despite the large number of patients investigated here in Europe for the assessment of travel-related illness, our work does not analyze all infectious illness in all returned patients. The results do not represent the broad spectrum of illness typically seen at nonspecialized primary care practice where mild or self-limited conditions would be found with higher frequency (*19*,*23*). The intake at sites reflects a mixed population of tertiary care and self-referred patients. Diagnoses that may be underrepresented include diseases of short incubation, many cases of which manifest during travel. However, GeoSentinel captures a sentinel sample of travelers; we have no reason to believe that cases we have not captured would have a different pattern of geographic acquisition than those in GeoSentinel. Also, we cannot relate our data collected on ill travelers to the total number of travelers to or from the area concerned. Because of this absence of denominator, incidence rates cannot be calculated or a numerical risk provided for travel to a particular destination. Absolute risk can be estimated only by monitoring cohorts prospectively, as was conducted in a few studies in the 1980s. Relatively small sample sizes and the limited number of destinations visited by travelers originating in 1 country are usually insufficient to elucidate destination-specific risk for individual diagnoses. Risk also could be calculated from the rate of illness in all travelers to each destination. However, capturing data on all ill travelers to just 1 destination, or even accurately ascertaining the denominator of all travelers to that destination, is not easily accomplished. No published studies have been able to describe this approach on a multicountry or worldwide basis.

However, given these caveats, the major strengths of our analysis are its focus on proportionate disease and the large numbers of patients in the database, which reduces the population-specific bias found in many smaller studies. Important published studies on several aspects of travel medicine have used the GeoSentinel database, now identified as a main source for the epidemiology of travel-related

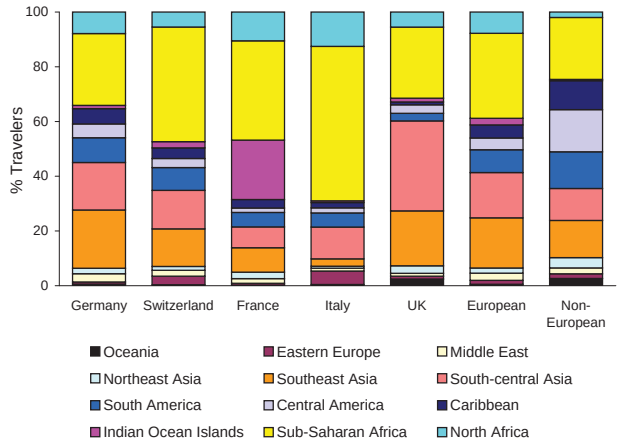

Figure 2. Regions visited by the 17,228 European travelers according to their countries of residence or citizenship. The right column presents these categories within the comparator groups of 12,663 non-European patients sampled from the GeoSentinel database (1997–2007).

illness (*18*,*19*,*24*–*27*). We selected and discussed specific syndromes and their causes. The European aspect of our study is unique.

Most patients in our survey were outpatients. Ubiquitous or cosmopolitan infections involving the skin and the respiratory, gastrointestinal, and urinary tracts were found frequently in our study as were imported tropical diseases (although the specific tropical/cosmopolitan disease ratio cannot be calculated accurately because etiolgoc agents were not systematically identified or recorded). As previously emphasized, healthcare providers should not overlook such cosmopolitan infections when examining patients returning from the tropics (*28*). Overall, of 10 ill European returned travelers, 4 had a gastrointestinal disorder, 2 experienced a febrile systemic illness, 2 sought treatment for a dermatologic problem, and 1 had a respiratory disease. Acute diarrhea is the most common travel-associated disease (*10*), and we show here that some destinations are more frequently associated with some specific causes. Also, all categories of European travelers to North Africa, south-central Asia, and the Middle East (but particularly classic tourist travelers) should be targeted for pretravel advice regarding diarrhea risk and self-treatment (*29*). Furthermore, the importance of respiratory diseases in travelers has been exemplified with clusters of measles after importation (*30*), and more recently, the emergence and global spread of influenza A pandemic (H1N1) 2009 virus (*9*). Moreover, seasonal influenza, which affects 5%–15% of the world's population annually and has been considered the second most frequent vaccine-preventable infection in travelers, is probably underestimated in returned travelers (*31*).

We highlight here that malaria remains the most common specific diagnosis in ill returned patients who have a systemic febrile illness (*23*). *P. falciparum* was the most commonly identified malaria species causing these infections, which mirrors situation in sub-Saharan Africa, a major source of malaria for European ill returned patients (*32*). The risk to travelers of acquiring malaria varies by destination. However, as shown here, the traveler profile also is an important determinant of malaria risk. *P. falciparum* malaria is a rare diagnosis among native Germans traveling for tourism but it is a frequent diagnosis among immigrant travelers from Italy and France who visit friends and relatives in sub-Saharan Africa and the Indian Ocean islands. As shown here, immigrant travelers (VFRs) rarely seek pretravel advice, and they are known to comply poorly with malaria chemoprophylaxis (*32*). Therefore, immigrant travelers represent a major group at risk for imported malaria in Europe, and an improved approach to educate this population about risks and prophylaxis needs to be developed.

Dengue is now considered one of the major causes of fever in ill returned travelers, who even may serve as important sentinels of new outbreaks of dengue in dengue-endemic areas (*33*). Here, dengue virus was the second most commonly identified pathogen responsible for fever, particularly in patients who returned from Southeast Asia. The incidence of dengue has been considered to be higher than

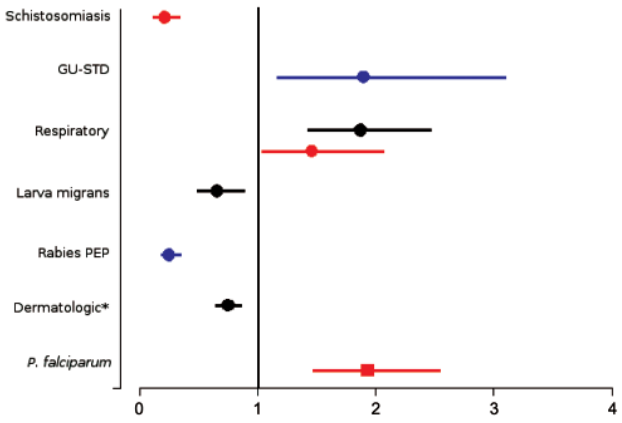

Figure 3. Odds ratios (ORs), European (n = 13,488) versus non-European (n = 6,900), by diagnosis and type of ill traveler, adjusted for travel duration. Each plot represents the estimated OR, and 95% confidence intervals are presented by lines. Only significant ORs based on the comparison of groups of >75 ill patients given a diagnosis are shown. The 3 main exposure regions are presented (Africa and Indian Ocean islands (red dots and square), South and Central America and Caribbean (black dots), Southeast and south-central Asia (blue dots). *All dermatologic diagnoses also include leishmaniasis, animal-related injuries requiring rabies post-exposure prophylaxis (PEP), and larva migrans. GU-STD, genitourinary and sexually transmitted diseases. Dots, classic tourist travelers; square, immigrant travelers visiting friends and relatives (VFRs).

that of other so-called typical travel-related diseases, such as vaccine-preventable hepatitis A and typhoid fever (*34*). Because of rapid, intercontinental transportation, European physicians now encounter patients with arbovirus infections that have short incubation periods, such as dengue, and patients who are still viremic. These factors raise the possibility of introducing the virus to non–dengue-endemic areas where competent vectors are prevalent, as was demonstrated for CHIKV in 2007 (*7*).

Some aspects described here may also influence medical practice that affects returned patients. For example, enteric fever caused by *Salmonella* infection was mainly observed in patients returning from south-central Asia, where multidrug resistance has been established and fluoroquinolone resistance is increasing (*35*).

Our results show the increasing importance of rickettsioses in ill returned travelers, particularly African tick-bite fever, which affects travelers to sub-Saharan Africa, especially those who go on safari and military personnel. These groups of travelers need to be singled out to receive advice on tick-bite prevention (*36*).

Our study also reinforces the view that dermatologic conditions are a leading cause of health problems in travelers (*37*). Pretravel advice should support the traveler's use of impregnated bed nets and repellents, promote the practice of efficient clothes drying and ironing to prevent myasis, and discourage direct contact of skin with wet soil to prevent larva migrans transmission.

Notably, a larger numbers of patients seeking rabies PEP were observed in France and the United Kingdom, where GeoSentinel clinics include rabies treatment centers. This highlights the potential for rabid animal–related injury in travelers, particularly in North Africa and the Middle East (*24*).

German ill travelers were overrepresented in our collective database because of the historical development of GeoSentinel and the predominance of Germans among European travelers. Furthermore, each GeoSentinel site has specific characteristics, and some would be considered as sentinel sites for diseases in specific categories of travelers returning from particular countries. For example, at the site in Marseille, France, the French colonial past has a large effect on the profile of imported disease. The city has the largest community of inhabitants from the Comoros Islands, Indian Ocean, including first- to third-generation migrants. Immigrant travelers (VFRs) from the Comoros Islands are major importers of *P. falciparum* malaria and were key to creating the initial alert about the CHIKV disease outbreak (*38*).

Differences in disease patterns between countries of origin may reflects national differences in the characteristics of the traveling population, the distribution of travel destinations, and referral and access to medical care. In addition, accommodation standards, eating habits, and other risk behavior at a given destination may reflect the national and cultural background of the traveler. These circumstances also apply when comparing European and non-European returned patients. However, although the non-European comparative group is heterogeneous, the diversity allows us to highlight some characteristics of European travel-related illnesses, such as the falciparum malaria within immigrant travelers (VFRs) in sub-Saharan Africa and the Indian Ocean islands. The economic situation of immigrants in Europe is unlikely to be as secure as that of second- or third-generation immigrants living in the United States, even if they have an easy access to the health system, including university hospitals in many cities. These factors, together with a higher likelihood of having severe imported diseases, such as malaria, may explain the high rate of immigrant travelers (VFRs) who were hospitalized. In Marseille, most of the immigrant travelers originating from Comoros claimed that some types of antimalarial chemoprophylaxis are too expensive for a whole family who travels every 2 years to visit friends and family.

European and non-Europeans ill returned travelers may also have a different code of conduct and behavior. For example, classic tourist travelers from Europe to Asia have a higher proportion of STDs than do other travelers. Again, our ill travelers probably do not reflect the whole population of travelers returning from the tropics with STDs because many probably consult their general practitioners first. However, a broad spectrum of STDs recently have been highlighted as common causes of health impairment among European travelers returning from the tropics, and Asia has destinations known for sex tourism (*39*).

Furthermore, depending on the destination, tourist travelers seem to be less frequently afflicted by diseases transmitted by contact of skin with fresh water or wet soil (schistosomiasis and larva migrans) and interaction with animals (animal-related injuries requiring rabies PEP); these facts suggest that they may be more compliant with travel health recommendations. We have no clear explanation, however, for the higher respiratory disease–related illnesses for European tourists traveling to Africa and America, but we note that SARS was imported to Europe in this way.

Conclusions

Clinicians encountering returned patients have an essential role in recognizing, and communicating travel-associated public health risks (*19*,*23*). In this context, surveillance in European travelers that encompasses a wide range of sites in Europe, including some with local specificity, is crucial to determine the epidemiology of travel-associated disease, to detect alarming events, and, if required, to or-

ganize a rapid response (*40*). Our combined European data can be used as background evidence for the practice of travel medicine in Europe.

These members of the GeoSentinel Surveillance Network also contributed data: François Chappuis, University of Geneva, Geneva, Switzerland; Giampiero Carosi, University of Brescia, Brescia, Italy; Fabrice Simon and Jean Delmont, Hôpital Nord, Marseille, France; Gerd-Dieter Burchard, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany; Rainer Weber and Robert Steffen, University of Zürich, Zürich, Switzerland; Mogens Jensenius, Ullevål University Hospital, Oslo, Norway; Effrossyni Gkrania-Klotsas, Addenbrooke's Hospital, Cambridge, UK; and Vanessa Field, InterHealth, London, UK. These additional members contributed data for Europeans nonresident in Europe: Prativa Pandey, Canadian International Water and Energy Consultants Clinic Travel Medicine Center, Kathmandu, Nepal; Susan MacDonald, Beijing United Family Hospital and Clinics, Beijing, People's Republic of China; Poh Lian Lim and Annelies Wilder-Smith, Tan Tock Seng Hospital, Singapore; Graham Brown, Joseph Torresi, Royal Melbourne Hospital, Melbourne, Victoria, Australia; Marc Shaw, Worldwise Travellers Health and Vaccination Centre, Auckland, New Zealand; Alejandra Gurtman, Mount Sinai Medical Center, New York City, New York, USA (2002 Oct–2005 Aug only); Robert Muller, Travel Clinic Services, Johannesburg, South Africa (2004 May–2005 Jun only); Phyllis E. Kozarsky and Carlos Franco-Paredes, Emory University, Atlanta, Georgia, USA; Jay S. Keystone and Kevin C. Kain, University of Toronto, Toronto, Ontario, Canada; Dominique Meisch, International SOS Clinic, Ho Chi Minh City, Vietnam; Robert Kass, Travellers Medical and Vaccination Centres of Australia, Adelaide, South Australia, Australia (1997 Dec–2001 Mar only); Eli Schwartz, Chaim Sheba Medical Center, Tel Hashomer, Israel; Bradley A. Connor, Cornell University, New York, New York, USA; N. Jean Haulman, Davie Roesel, and Elaine C. Jong, University of Washington, Seattle, Washington, USA; Watcharapong Piyaphanee and Udomsak Silachamroon, Mahidol University, Bangkok, Thailand; R. Bradley Sack and Robin McKenzie, Johns Hopkins University, Baltimore, Maryland, USA (1997 Dec–2007 Aug only); Cecilia Perret and Francisca Valdivieso, Pontificia Universidad Católica de Chile, Santiago, Chile; Sarah Borwein, Central Health Medical Practice, Hong Kong SAR, China; Carmelo Licitra and Antonio Crespo, Orlando Regional Health Center, Orlando, Florida, USA; Lin H. Chen and Mary E. Wilson, Harvard University, Cambridge, Massachusetts, USA; Thomas B. Nutman and Amy D. Klion, National Institutes of Health, Bethesda, Maryland, USA; Vernon Ansdell, Kaiser Permanente, Honolulu, Hawaii, USA (1997 Oct–2003 Jan only); DeVon C. Hale and Stefanie S. Gelman, University of Utah, Salt Lake City, Utah, USA; and Hiroko Sagara, Yokohama Municipal Citizen's Hospital, Yokohama, Japan.

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Multicenter GeoSentinel Analysis of Rickettsial Diseases in International Travelers, 1996–2008

Mogens Jensenius, Xiaohong Davis, Frank von Sonnenburg, Eli Schwartz, Jay S. Keystone, Karin Leder, Rogelio Lopéz-Véléz, Eric Caumes, Jakob P. Cramer, Lin Chen, and Philippe Parola, for the GeoSentinel Surveillance Network[1]

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the most common rickettsial diseases in returning international travelers between 1996 and 2008.
- Identify risk factors associated with higher likelihood of rickettsial disease among returning international travelers.
- Describe the most common treatment for rickettsial diseases.

Editor

Nancy Farm Männikkö, PhD, Technical Writer-Editor, *Emerging Infectious Diseases. Disclosure: Nancy Farm Männikkö, PhD, has disclosed no relevant financial relationships.*

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We investigated epidemiologic and clinical aspects of rickettsial diseases in 280 international travelers reported to the GeoSentinel Surveillance Network during 1996–2008. Of these 280 travelers, 231 (82.5%) had spotted fever (SFG) rickettsiosis, 16 (5.7%) scrub typhus, 11 (3.9%) Q fever, 10 (3.6%) typhus group (TG) rickettsiosis, 7 (2.5%) bartonellosis, 4 (1.4%) indeterminable SFG/TG rickettsiosis, and 1 (0.4%) human granulocytic anaplasmosis. One hundred ninety-seven (87.6%) SFG rickettsiosis cases were acquired in sub-Saharan Africa and were associated with higher age, male gender, travel to southern Africa, late summer season travel, and travel for tourism. More than 90% of patients with rickettsial disease were treated with doxycycline, 43 (15.4%) were hospitalized, and 4 had a complicated course, including 1 fatal case of scrub typhus encephalitis acquired in Thailand.

Rickettsial diseases are acute and potentially severe zoonotic infections caused by obligate intracellular,

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gram-negative bacteria belonging to the order Rickettsiales. The taxonomy of Rickettsiales is complex and continues to be updated, but currently the agents of rickettsial diseases are classified as belonging to 4 distinct genera: *Rickettsia* (including 2 biogroups: spotted fever group [SFG] rickettsiae with >10 species and typhus group [TG] rickettsiae with 2 species), *Orientia* (*Orientia tsutsugamushi*, the agent of scrub typhus), *Ehrlichia* (*Ehrlichia chaffeensis,* the agent of human monocytic ehrlichiosis), and *Anaplasma* (*Anaplasma phagocytophilium*, the agent of human granulocytic anaplasmosis). Diseases caused by *Rickettsia* and *Orientia* species are often collectively referred to as rickettsioses. *Coxiella burnetii*, the agent of Q fever, and *Bartonella* spp. were recently removed from the order Rickettsiales, but Q fever and bartonelloses are still frequently categorized as rickettsial diseases (*1*).

Rickettsial diseases are increasingly being recognized among international travelers (*2*). A recent study of ≈7,000 returnees with fever as a chief reason to seek medical care suggests that 2% of imported fevers are caused by rickettsioses and that 20% of these patients are hospitalized (*3*). Most cases are acquired in sub-Saharan Africa, where SFG rickettsioses are second only to malaria as the most commonly diagnosed diseases in returnees with systemic febrile illness (*4*). With few exceptions, however, our knowledge of the incidence rates, associated factors, signs, symptoms, and outcome of rickettsial diseases in travelers is rudimentary and mostly based on smaller case series. We report all cases of rickettsial diseases in returned travelers reported to the GeoSentinel Surveillance Network from June 1996 through December 2008.

Materials and Methods

Data Source

GeoSentinel is a global network aimed at surveying ill international travelers and was established in 1995 through the International Society of Travel Medicine and the Centers for Disease Control and Prevention. The 41 current GeoSentinel sites contribute clinician-based, anonymous information on all ill travelers seen that is entered in a structured query language database at a central data center. Data collected include demographic information, recent travel history, reason for travel, outpatient or inpatient status, whether the patient was seen during or after travel, whether the patient traveled independently versus organized travel (i.e., travel with a tour group), whether the patient had pretravel encounter with a healthcare provider, patient symptoms, and diagnosis. All GeoSentinel sites use the best reference diagnostic methods available in the country where the site is located. The diagnosis, which may be reported as confirmed, probable, or suspected, is chosen from a standardized list of >500 possible etiologic and syndromic diagnoses, 11 of which refer to rickettsial diseases. Patients may receive several diagnoses, some of which describe well-known complications of rickettsial diseases, e.g., acute renal failure, acute encephalitis, acute respiratory distress syndrome, and death (*3*,*4*). The GeoSentinel questionnaire does not contain queries about case management, but in December 2008 all sites were requested to estimate the percentage of their patients with rickettsial diseases who received treatment with antirickettsial drugs (e.g., doxycycline) during the study period.

Inclusion Criteria and Definitions

Data entered into the GeoSentinel database from June 1996 through December 2008 were reviewed. Only travelers seen with confirmed or probable diagnoses were included in the analysis. Cases of rickettsial diseases were defined according to the criteria mentioned below. A subanalysis, comparing SFG rickettsioses with other diseases in ill returnees from sub-Saharan Africa, was also performed (Figure 1).

A microbiologic diagnosis of recent rickettsial disease was in most cases based on immunofluorescence antibody (IFA) tests and, occasionally, on PCR and Western blot. Diagnostic criteria of recent infection by IFA tests were either a 4-fold increase of immunoglobulin (Ig) G or IgM titers in paired serum samples drawn ≥10 days apart, or elevated IgG and/or IgM titers in single samples consistent with recent infection as interpreted by the local microbiology laboratory. Because IFA tests cannot distinguish between species within the same *Rickettsia* biogroup, diseases caused by *Rickettsia* species were dichotomized as SFG rickettsiosis and TG rickettsiosis.

We included all cases of confirmed rickettsial disease defined as a traveler with pertinent travel history and clinical signs, and microbiologic test results supporting recent infection. For SFG rickettsiosis and scrub typhus we also

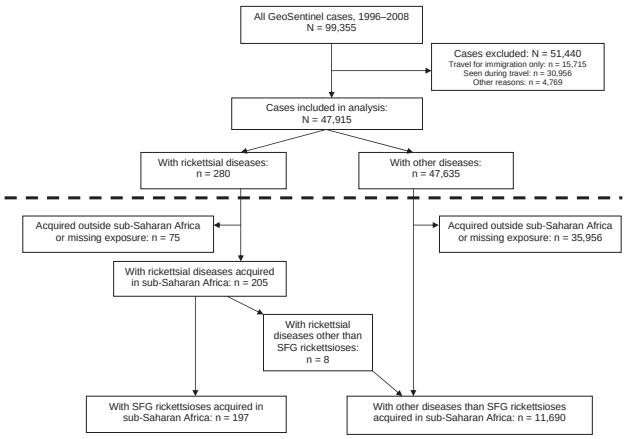

Figure 1. Study design with main study (above dotted line) and substudy (below dotted line) of spotted fever group (SFG) rickettsiosis acquired in sub-Saharan Africa, 1996–2008.

included probable cases defined as a traveler with pertinent travel history and clinical signs including ≥1 inoculation eschars, and inconclusive or unavailable microbiologic test results. Cases were categorized in 9 disease groups: SFG rickettsiosis, TG rickettsiosis, indeterminate SFG/TG rickettsiosis (defined as cases in whom neither clinical signs nor microbiologic tests could distinguish between SFG and TG rickettsiosis), scrub typhus, ehrlichiosis, anaplasmosis, acute and chronic Q fever (based on the presence of antibodies to the 2 distinct antigenic phases of *C. burnetii* by IFA test [5]), and bartonellosis. Countries were grouped according to the United Nations region system, and for sub-Saharan Africa also in subregions; for clarification, the southern Africa subregion included Botswana, Lesotho, Namibia, South Africa, and Swaziland. Classification of reason for travel related to current illness was grouped into 4 categories: tourism, business, visiting friends and relatives, and other reason, which included studies or military, missionary, or foreign aid deployment.

Statistical Analysis

All data were analyzed using SAS software, version 9 (SAS Institute, Cary, NC, USA). Comparison of travelers to sub-Saharan Africa with SFG rickettsioses with all other ill travelers to the same destination used the Student *t* test for continuous variables and Cochran-Mantel-Haenszel statistic for binary variables. The association between possible risk factors and a diagnosis of SFG rickettsioses acquired in sub-Saharan Africa was measured with odds ratios and 95% confidence intervals. Variables included in the univariate analysis were mean age, male gender, travel to southern Africa, travel from March through May, travel >1 week, no pretravel clinic visit, independent travel, and tourism as reason for travel. Variables with a p value <0.05 in the final multivariate logistic regression model were considered significant.

Proportionate morbidity for SFG rickettsiosis acquired in sub-Saharan Africa was defined as the number of cases as a proportion of all ill returned travelers from the region. Analysis of case reports over time was based on monthly proportionate morbidity, i.e., the number of patients with SFG rickettsiosis as a proportion of the number of all ill returned travelers attending any GeoSentinel site in that month. The monthly seasonality was based on aggregate data for that month over all years. The annual proportionate morbidity for SFG rickettsiosis acquired in southern Africa from 1999 through 2008 was estimated in a similar way based on relevant cases for each year. The Cochran-Armitage test was used for testing trend over years. This statistic tests for trend in binomial proportions across levels of a single factor or covariate and is appropriate for a contingency table where the response variable has 2 levels and the explanatory variable is ordinal. A 1-sided p value <0.05 would indicate a decreasing (with a negative statistic) or increasing (with a positive statistic) trend.

Results

We identified 99,355 travelers who sought medical care at a GeoSentinel site during June 1996–December 2008. Among the 47,915 case-patients who met the study inclusion criteria, 280 (0.6%) had a diagnosis of rickettsial disease (Figure 1); among those having fever, the proportion was 211/13,763 (1.5%). Of travelers with rickettsial disease 231 (82.5%) had SFG rickettsioses, 16 (5.7%) scrub typhus, 11 (3.9%) acute Q fever, 10 (3.6%) TG rickettsioses**,** 7 (2.5%) bartonelloses, 4 (1.4%) indeterminate TG/SFG rickettsioses, and 1 (0.4%) human granulocytic anaplasmosis; there were no cases of chronic Q fever and ehrlichiosis. Cases were reported from 32 of the 41 active GeoSentinel sites: a total of 154 (54.9%) were reported from sites in Europe, 77 (27.5%) from North America, 17 (6.0%) from New Zealand/Australia, and 32 (11.6%) from Asia, including the Middle East. Most cases were associated with travel to sub-Saharan Africa (75.1%) (Table 1). A pretravel encounter with a healthcare provider was reported in 157 cases (58.4%). At least 90% of cases of rickettsial diseases were estimated to have been treated with antirickettsial drugs (doxycycline in most cases, occasionally a flouroquinolone) at the reporting sites during the study period.

SFG Rickettsioses

Of the 231 cases of SFG rickettsioses (146 confirmed and 85 probable) a total of 136 (58.9%) were men; the mean age was 43.4 years (median 45 years, range 33–53 years). Tourists comprised 182 (78.8%), 28 (12.1%) had traveled for business, 6 (2.6%) were visiting friends and relatives, and 14 (6.1%) had traveled for other reasons. One hundred ninety-seven (87.6%) case-patients were infected in sub-Saharan Africa; South Africa (n = 135), Zimbabwe (n = 13), and Tanzania (n = 7) were the 3 most commonly reported countries of exposure (Table 1). The median time from travel to reporting to a GeoSentinel site was 8 days (range 4–12 days). Two case-patients, a 23-year-old French woman tourist to Mongolia in June 2008, and a 27-year-old Swiss woman student traveler to Corsica, France, in October 2008, were infected by *Rickettsia slovaca* confirmed by PCR and Western blot. There were no deaths among the travelers with SFG rickettsioses, but 22 (9.6%) were hospitalized, and multiorgan failure with acute respiratory distress syndrome developed in 2 Israeli men 47 and 73 years of age, respectively, after they traveled to India in October 2004.

Analysis of demographic and exposure variables for the 197 travelers to sub-Saharan Africa with SFG rickettsiosis compared with 11,690 travelers to the same region with other diagnoses is shown in Table 2. A multi-

Table 1. Travel destinations of 280 travelers with rickettsial diseases, by destination and disease, as reported to GeoSentinel, 1996–2008*

Destination	No. travelers						
	SFG rickettsiosis	TG rickettsiosis	Indeterminate SFG/TG rickettsiosis	Scrub typhus	Anaplasmosis	Acute Q fever	Bartonellosis
Western Europe	7	1			1	2	1
Eastern Europe			1				
North Africa	3						
Sub-Saharan Africa	197	1				5	1
Middle East	1					2	1
Northeast Asia	2	1				1	
South central Asia	5	1	1	5			
Southeast Asia	3	6	2	9			1
Australia/New Zealand	1			1			
Oceania	1						
North America	1						
Central America	3						
Caribbean	1						3
South America							
Unknown	6			1		1	
Total	231	10	4	16	1	11	7

*SFG, spotted fever group; TG, typhus group.

variate logistic regression model was performed to analyze the effects on SFG rickettsiosis of risk factors including age, gender, travel to southern Africa, travel from March to May, travel duration longer than 7 days, no pretravel clinic visit, independent travel, and travel for tourism. Older age, male gender, travel to southern Africa, travel from March to May, and travel for tourism were found to be independently associated with SFG rickettsiosis. An analysis of monthly proportionate morbidity identified a peak of cases in March, April, and May (Figure 2). The proportionate morbidity of cases with SFG rickettsiosis in ill returnees from southern Africa from 1999 through 2008 was 139/1,017 (13.7%). The overall Cochran-Armitage trend test did not show statistically significant change (p = 0.877, by 2-sided trend test). As shown in Figure 3, the annual proportionate morbidity increased and decreased twice over the years and did not maintain a monotone increasing or decreasing pattern.

Other Rickettsial Diseases

The 10 travelers with TG rickettsiosis, of whom 6 were men, had a mean age of 28.0 years (median 25.5 years,

Table 2. Univariate and multivariate analyses of risk factors associated with SFG rickettsiosis in travelers to sub-Saharan Africa, 1996–2008*

Variable	Travelers with SFG rickettsiosis, N = 197†	Travelers without SFG rickettsiosis, N = 11,690†	Univariate association		Multivariate model‡	
			OR (95% CI)	p value	OR (95% CI)	p value
Mean age, y	43.9, n = 196	36.5, n = 11,608	–	<0.0001	1.02 (1.01–1.03)§	<0.0001
Male gender, no. (%)	115 (58.4), n = 197	6,105 (52.6), n = 11,599	1.26 (0.95–1.68)	0.11	1.40 (1.02–1.92)	0.035
Travel to southern Africa,¶ no. (%)	139 (70.6), n = 197	759 (6.5), n = 11,686	34.5 (25.18–47.28)	<0.0001	23.61 (16.86–33.07)	<0.0001
Travel in late summer,# no. (%)	89 (47.1), n = 189	4,220 (40.6), n = 10,402	1.30 (0.98–1.74)	0.07	1.57 (1.15–2.15)	0.005
Travel duration >7 d, no. (%)	173 (91.5), n = 189	9,661 (92.9), n = 10,402	0.83 (0.49–1.39)	0.48	0.67 (0.38–1.18)	0.164
No pretravel clinic visit, no. (%)	40 (21.7), n = 184	2,823 (26.5), n = 10,665	0.77 (0.54–1.10)	0.15	0.98 (0.66–1.44)	0.903
Independent travel,** no. (%)	34 (44.2), n = 77	4,100 (58.6), n = 6,993	0.56 (0.35–0.87)	0.01	0.83 (0.56–1.25)	0.373
Tourism as reason for travel, no. (%)	163 (82.7), n = 197	5,027 (43.0), n = 11,686	6.35 (4.38–9.21)	<0.0001	2.96 (1.97–4.45)	<0.0001

*SFG, spotted fever group; OR, odds ratio; CI, confidence interval.
†n = number of travelers for whom this information was available.
‡This model included all variables considered at univariate level because of their clinical relevance. The Hosmer and Lemeshow goodness-of-fit test for this model is p = 0.575.
§Odds ratio is for 1-y increase in age.
¶United Nations subregion comprising Botswana, Lesotho, Namibia, South Africa, and Swaziland.
#March–May.
**Independent travel was not formally collected by GeoSentinel until after May 2007.

range 20–50 years). Four case-patients were tourists, 2 were visiting friends and relatives, 1 was a business traveler, and 3 had traveled for other purposes. Southeast Asia, including 3 travelers infected in Indonesia, was the most common region of exposure (Table 1). The median time from travel to reporting a site was 6 days (range 3–14 days). Five patients were hospitalized and no complications were noted. One patient, a 23-year-old Japanese man visiting friends and relatives in Bali, Indonesia, had *R. typhi* infection confirmed by PCR.

Indeterminate SFG/TG rickettsiosis was diagnosed in 4 male tourists, 15, 50, 51, and 67 years of age, respectively. Two case-patients were infected in Southeast Asia (Table 1). No complications were recorded.

The 16 travelers with scrub typhus (5 confirmed and 11 probable), of whom 10 were men, had a mean age of 36.6 years (median 32.5 years; range 26–67 years). Nine patients were infected in Southeast Asia (including Thailand, n = 4) and 5 in south-central Asia (including India, n = 3). Twelve patients were tourists, 1 was visiting friends and relatives, and 3 had traveled for business. The median time from travel to reporting to a GeoSentinel site was 9 days (range 2–25 days). Six case-patients were hospitalized. Encephalitis developed in 2 Singaporean travelers: a 42-year-old man, a tourist infected in Thailand in December 2007, died, and a 51-year-old man infected in Taiwan while traveling on business in April 2008 survived.

An uncomplicated case of human granulocytic anaplasmosis was seen in August 2008 in a 32-year-old US woman tourist to the Netherlands. The diagnosis was based on detection of intracellular morulae.

The 11 travelers with acute Q fever, including 4 men, had a mean age of 53.0 years (median 59 years; range 20–64 years). Sub-Saharan Africa, including 2 case-patients infected in Tanzania, was the most common region of exposure (Table 1). Seven patients were tourists, 3 were business travelers, and 1 had traveled for other reasons. The median time from travel to reporting to a site was 21 days (range 5–52 days). Isolated fever (n = 7) and respiratory symptoms (n = 4) were the most common clinical manifestations. Four patients were hospitalized. All 11 patients with Q fever had uncomplicated clinical courses.

The 7 travelers with bartonellosis, including 3 males, had a mean age of 33.6 years (median 32 years, range 9–56 years). Three patients were infected in the Caribbean (Table 1). Four were tourists and 3 had traveled for other purposes. The median time from travel to reporting to a GeoSentinel site was 25 days (range 7–39 days). *Bartonella henselae* infection was diagnosed in all case-patients by serologic or immunohistochemical analysis. Six travelers had uncomplicated cat-scratch disease, and 1 had bacillary angiomatosis.

Discussion

This study of 280 case-patients conducted over >12 years at 32 institutions on 5 continents represents the largest series of imported rickettsial diseases published to date. Noteworthy, SFG rickettsiosis was by far the most commonly diagnosed group of disease in our study. Numerous SFG rickettsioses occur throughout the world, the most important being Mediterranean spotted fever (with its variants Indian tick typhus, Astrakhan fever, and Israeli spotted fever) caused by *R. conorii conorii*, Rocky Mountain spotted fever caused by *R. rickettsii*, and African tick bite fever caused by *R. africae* (*1*). Some SFG rickettsioses may be accompanied by severe complications (*6*,*7*), as was exemplified by our 2 case-patients infected in India, possibly representing Indian tick typhus caused by *R. conorii indica* (*8*). Tick-borne lymphadenopathy (TIBOLA) caused by *R. slovaca*, a recently described entity associated with *Dermacentor* ticks and characterized by inoculation eschar, fatigue, and painful regional lymphadenitis (*9*), was diagnosed in 2 of our travelers. Being well documented across southern and central Europe, and especially so in children (*10*), our traveler infected in Mongolia represents the first documented case of TIBOLA acquired in Asia and illustrates how travel medicine may help identify new areas of endemicity for infectious diseases.

As shown here and by others (*11*), most cases of travel-associated SFG rickettsiosis are acquired in sub-Saharan Africa, and particularly in South Africa and neighboring countries. In the present series, as many as 13.7% of all healthcare-seeking returnees from southern Africa had a diagnosis of SFG rickettsiosis (Figure 3). Although several pathogenic SFG rickettsiae have been described in sub-Saharan Africa, including *R. conorii*, *R. siberica*, and

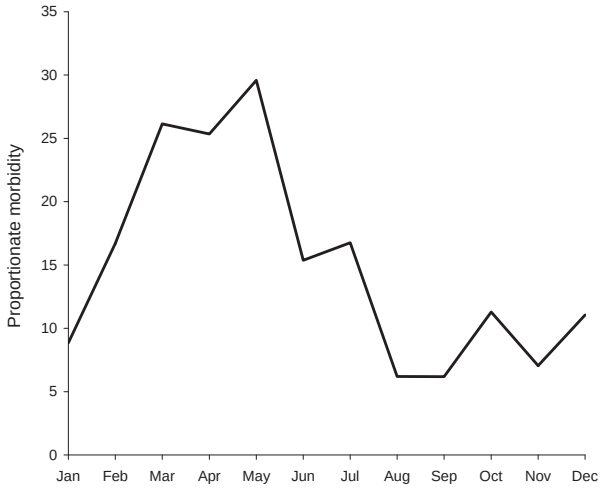

Figure 2. Monthly proportionate morbidity (no. cases/1,000 travelers) of spotted fever group rickettsiosis acquired in sub-Saharan Africa, 1996–2008.

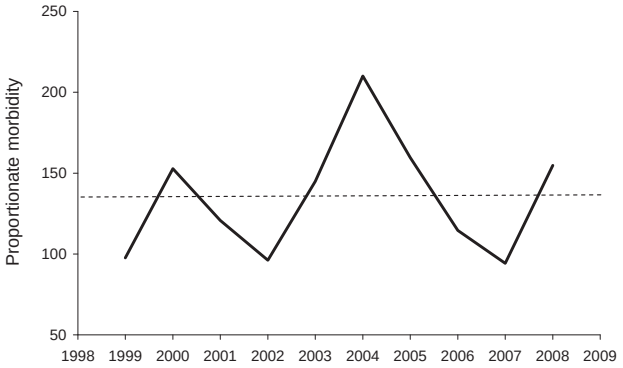

Figure 3. Annual proportionate morbidity (no. cases/1,000 travelers) of spotted fever group rickettsiosis acquired in southern Africa, 1996–2008. The dotted line indicates the mean value of 137/1,000 (13.7%).

R. aeschlimannii (*12*), 2 recent series evaluating 159 case-patients with species-specific tests, including PCR and Western blot, suggest that >99% of SFG rickettsioses diagnosed in international travelers to the region are caused by *R. africae* (*13*,*14*). In 1 of these reports, game hunting as reason for travel, travel to southern Africa, and travel during the summer season from November through April were found to be independent risk factors (*14*). If one assumes that most, if not all, of our 197 cases of SFG rickettsioses acquired in sub-Saharan Africa were de facto African tick bite fever, the present study suggests additional risk factors for this disease: male gender, higher age, travel during the late summer months of southern Africa (i.e., March–May; Figure 2), and travel for tourism. Although African tick bite fever is usually benign and self-limited, some patients may develop debilitating complications such as reactive arthritis, cranial and peripheral neuropathies, myocarditis, and neuropsychiatric symptoms, or experience a long-lasting convalescence, the latter phenomenon recently reported in elderly patients (*15–17*).

Our series comprises 10 cases of TG rickettsioses, all of which were considered to represent murine typhus caused by *R. typhi*, a bacteria transmitted from rodents to humans by rat fleas in many tropical and subtropical areas. Murine typhus is sometimes reported in returnees from the Mediterranean basin, Asia, and Africa; typical itineraries included travel to port cities or beach resorts (*18*,*19*). As in the present series, most infected travelers have mild disease with fever and constitutional symptoms, but complicated cases, including deaths, have been reported by others (*20*).

We also identified 16 cases of scrub typhus, a common disease in rural south and Southeast Asia and the Pacific. Before the present report, <30 cases of travel-associated scrub typhus had been published in the literature, and infection was predominantly acquired in Thailand and neighboring countries (*21*). The disease is transmitted by the bites of larval trombiculid mites (chiggers) that occur year round on grassy vegetation and is typically acquired by campers, trekkers, and visitors to rice paddies (*2*). Although most cases in travelers are mild and uncomplicated, scrub typhus may, as exemplified here, result in life-threatening encephalitis (*22*).

Human granulocytic anaplasmosis is a usually mild and nonspecific febrile illness commencing a few days after an *Ixodes* tick bite (*23*). It is endemic in North America and Europe with a geographic distribution that largely coincides with that of Lyme borreliosis. Human granulocytic anaplasmosis is rarely reported in international travelers but was recently diagnosed in an Austrian tourist visiting Slovenia (*24*). Our patient acquired the disease in 2008 in the Netherlands, where the first domestic case was reported in 1999 (*25*).

The ubiquitous Q fever, a zoonosis typically transmitted from domesticated mammals to humans by contaminated aerosols, is occasionally found in international travelers (*26*). Many infected travelers can recall visits to local farms and direct physical contact with domestic animals (*27*). All of our 11 case-patients had uncomplicated acute Q fever, the typical clinical sign in travelers, and most had a nonfocal febrile illness. However, it should be noted that acute Q fever may be severe and even fatal in travelers (*28*).

Bartonelloses are rarely reported in travelers but cases of Carrion disease caused by *Bartonella bacilliformis* have been seen after travel to South America (*29*,*30*). In the present series, we identified 7 case-patients likely having *B. henselae* infection, a ubiquitous condition associated with felines and their fleas and not previously reported in international travelers. Six of our patients had cat-scratch disease, a self-limiting disease characterized by cutaneous papules or pustules at the site at the inoculation site and an often long-lasting painful regional lymphadenitis, and 1 patient had bacillary angiomatosis, a potentially severe condition with vascular proliferation in the skin and internal organs (*31*).

With an overall incidence rate of 0.6% (and 1.5% of those travelers with fever), our analysis suggests that rickettsial diseases are uncommon in ill returnees. However, underdiagnosis is likely to be widespread, even at specialized institutions such as those associated with the GeoSentinel surveillance network. Few specific clinical signs exist in rickettsial diseases. Many cases have a nonfocal febrile disease of mild-to-moderate severity, accompanied by nonspecific results in routine blood tests (*32*). The inoculation eschar, a painless black skin lesion surrounded by a red halo that develops at the site of the infective tick or mite bite, is a useful diagnostic clue in SFG rickettsioses and scrub typhus, but may be absent in ≤40% of such

cases (*14*). The available array of microbiologic diagnostic tests is another predicament in the management of rickettsial diseases. Although sensitive and specific techniques, such as PCR and culture, can be performed at reference centers, most cases worldwide are diagnosed by serologic analysis (*1*). The principal limitations with serologic analysis include a usually negative result in the acute phase when most patients first seek medical care, poor sensitivity in cases treated early with doxycycline, and an inability to distinguish between the various *Rickettsia* species caused by cross-reactions (*33*,*34*).

Some rickettsial diseases are potentially malignant, but severe complications developed in only a few patients in the present series, and only 1 traveler died. There may be several reasons for this favorable outcome, including a large percentage of benign African tick bite fever cases, and a widespread empiric use of antirickettsial drugs in cases of suspected rickettsial disease. It is noteworthy that rickettsial organisms are inherently resistant to many antimicrobial drugs commonly used as treatment for acute fevers, including the β-lactams, and treatment of choice is tetracyclines, in particular, doxycycline. Fluoroquinolones and newer macrolides may also be useful (*1*,*35*).

Our study had limitations similar to those in other GeoSentinel studies, including a possible selection bias towards complicated and unusual cases (*3*,*4*). Also, because rickettsial diseases, with the major exceptions of Q fever and bartonelloses, have short incubation periods (typically around 1 week) some cases are likely to manifest during travel and may be seen only by foreign healthcare providers. An analysis solely based on persons reporting posttravel is thus likely to underestimate the true incidence of rickettsial diseases in international travelers. However, because GeoSentinel currently has no site in sub-Saharan Africa, the prime destination for cases of travel-associated rickettsial diseases, we chose to exclude cases seen during travel from the analysis. Lastly, because most ill returnees seen at GeoSentinel sites have traveled to the tropics, we may have underestimated the incidence of rickettsial diseases typically acquired in temperate areas, including Rocky Mountain spotted fever, TIBOLA, and Mediterranean spotted fever.

In summary, the present study demonstrates the wide spectrum of rickettsial diseases that may be encountered in international travelers. Most infections are acquired in sub-Saharan Africa, where African tick bite fever is the predominate disease. The overall outcome is favorable but, because some rickettsial diseases may take a dire course, empirical treatment with an antirickettsial drug should always be considered whenever evaluating a traveler with an otherwise unexplained febrile disease who has recently returned from areas where these diseases are endemic.

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Burkholderia pseudomallei Misidentified by Automated System

Christoph Weissert, Günter Dollenmaier, Philippe Rafeiner, Julia Riehm, and Detlev Schultze

After returning from Thailand, a 35-year-old man from Switzerland was hospitalized with an abscess of the head. Material cultured from the abscess and adjacent bone grew a gram-negative rod, which was misidentified by an automated microbiology system as *Burkholderia cepacia*. The organism was eventually identified by molecular methods as *B. pseudomallei*.

Burkholderia pseudomallei, the etiologic agent of melioidosis, can cause pyogenic or granulomatous lesions and is endemic to tropic regions, mainly in Southeast Asia and northern Australia. This organism is a potential category B bioterrorism agent (*1*). Melioidosis occurs sporadically in travelers returning from disease-endemic areas, and laboratories in regions where this disease is not endemic are not familiar with identification of *B. pseudomallei*, thus potentially leading to misidentification (*2*). We report the misidentification of this organism by an automated microbiology system.

The Study

On August 20, 2008, a 35-year-old man from Switzerland was admitted to the Cantonal Hospital in St. Gallen, Switzerland. He had extradural cranial abscess of the right parietal area and a defect in adjacent bone. In May and June 2008, he traveled to Singapore and Malaysia (Kuala Lumpur and the Perhentian Islands), then to southwestern (Ko Samui, Ko Tau) and northern (Chiang Mai) Thailand where he went trekking and river rafting.

The patient did not remember receiving a head injury during his trip. Seventeen days after returning to Switzerland, he had a swelling in the right parietal area of the head. The parietal bulge increased, but puncture by his general practitioner showed no aspirate. During the next 7 weeks, the bulge became painful and secretion of pus was noted at the time of admission.

At admission, his general condition was good and he had no signs of systemic inflammation. He did not have any neurologic deficits or other abnormal findings. Test results for complete blood cell count, C-reactive protein and creatinine levels, and liver functions were normal. Computed tomography and magnetic resonance imaging of the head showed the abscess and a small defect of bone (Figure). The abscess and part of the cranial bone were then surgically removed.

Culture material from the abscess and biopsy specimens of the abscess capsule and the cranial bone grew gram-negative, oxidase-positive rods, and smooth creamy colonies on sheep blood agar after incubation for 48 hours at 35°C. For identification, a suspension of the isolate was prepared and tested in a UNMIC/ID-62 panel of the BD Phoenix Automated Microbiology System (Becton Dickinson AG, Allschwil, Switzerland) per the manufacturer's instructions. This system identified the isolate as *B. cepacia* (99% confidence). When a species is identified with >90% confidence, the Phoenix System gives an identification result as a measure of likelihood that the identification is the only correct one.

The patient was discharged from hospital after 5 days with a preliminary diagnosis of *B. cepacia* infection of soft tissue (the cranial bone lesion was attributed to trauma). He was treated with oral cotrimoxazole (160/800 mg 2× a day) for 16 days. The isolate was sensitive to cotrimoxazole (MIC = 1 mg/L for trimethoprim and 19 mg/L for sulfamethoxazole) by the Phoenix System for *B. cepacia* (Becton Dickinson). The isolate was sensitive to imipenem, ceftazidime, doxycycline, cotrimoxazole, and tetracycline by Etest (AB Biodisk, Solna, Sweden).

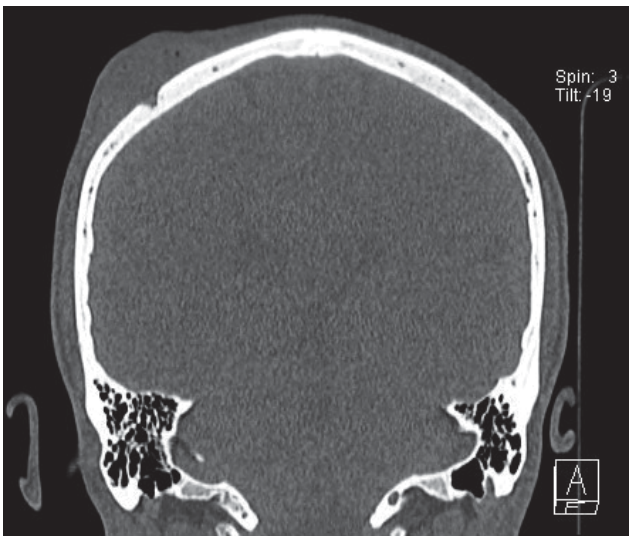

Figure. Computed cranial tomography image of the patient showing a swelling at the right parietal area and a small defect of the bone.

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The diagnosis was regarded as preliminary for the following reasons. First, identification of *B. cepacia* by common automated identification instruments such as the Phoenix System or VITEK 2 (bioMérieux, Geneva, Switzerland) requires confirmatory identification by molecular tests (*3*). Second, an abscess is an uncommon location for *B. cepacia* (*4*). Third, the bacterial colonies emitted an unexpected, earthy odor. Fourth, the isolate was sensitive to amoxicillin (MIC = 8 mg/L) and clavulanate (MIC = 4 mg/L).

To verify identification of the isolate, a 500-bp fragment of the 16S rRNA gene was amplified and sequenced by using the Fast MicroSeq 500 16S rDNA Bacterial Identification Kit and a PRISM 310 Genetic Analyzer (both from Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Sequence analysis was performed by using MicroSeq ID Microbial Identification Software (Applied Biosystems). The MicroSeq ID 2.0 500-bp library identified *B. pseudomallei* (ATCC 23343, gb DQ108392.1) with a 446-bp consensus length and 1 mismatch with *B. mallei* (NCTC 10247, gb CP000548.1). These results suggested that our isolate was *B. pseudomallei*.

Additional investigations with a flagellin C gene–specific real-time PCR (*5*) suggested that the isolate was *B. pseudomallei* or *B. mallei*. Multilocus sequence typing (*6*) showed the allelic profile 1/2/3/1/1/2/1, which identified the isolate as *B. pseudomallei* sequence type 306. This sequence type was isolated from serum samples of 2 patients in Thailand with invasive melioidosis in 1991 and 2006.

Forty-four days after surgery, new biopsy specimens of soft tissue below the parietal scar and a sample of galea aponeurotica were cultured for *B. pseudomallei* after the patient received 2 weeks of inadequate therapy with low-dose cotrimoxazole to determine its drug resistance pattern. Cultures yielded only *Staphylococcus epidermidis*, which was regarded as a contaminant. To ensure eradication of *B. pseudomallei*, the patient was treated with imipenem (500 mg, 4×/day), cotrimoxazole (400 mg trimethoprim/day), and leucovorine (15 mg, 3× a week) for 2 weeks and later with cotrimoxazole (320 mg trimethoprim/day) and leucovorine (15 mg, 3×/week) for 6 months. The patient recovered after 6 months; he had a small indentation without signs of inflammation at the site of the abscess.

For comparison with the Phoenix System, we retrospectively analyzed the isolate by using the API 20NE biochemical test panel V7.0 (bioMérieux). This panel identified the isolate as *B. pseudomallei* (profile 1156577; 99.9% ID, 1.0 T).

Conclusions

Automated methods for identification of bacterial isolates and testing of antimicrobial drug susceptibility, such as the Phoenix System, have become standard in most clinical laboratories because they are easy to use and turnaround time is rapid. The Phoenix System uses fluorogenic and chromogenic substrates for its identification algorithms, a broth-based antimicrobial drug–susceptibility testing method, and a data-processing application (Phoenix EpiCenter; Becton Dickinson AG). Unfortunately, *B. pseudomallei* was not in the database of this system, which led to misidentification of our isolate as *B. cepacia*. Failure to correctly identify *B. pseudomallei* has also been reported with another widely used automated system, the Vitek2 system (*7*). To identify isolates from patients traveling to disease-endemic areas, automated systems should be updated for identification of *B. pseudomallei* and other rare bacteria that cause severe human infections, are hazardous to laboratory personnel, and may be used as bioterrorism agents (e.g., *Brucella* spp. and *B. mallei*).

Three modes of acquisition (inhalation, ingestion, and inoculation) are recognized for *B. pseudomallei* infection. Skin and soft tissue infections may occur after minor wounds or from hematogenous spread (*8*). In our patient, inoculation of the skin with *B. pseudomallei* after a minor injury in Thailand is probably the mode of infection.

Although laboratory personnel handled cultures of *B. pseudomallei* for identification and drug resistance testing and smelled culture plates without knowing the isolate's identity, none became ill or showed signs of melioidosis. According to expert consensus (*9*), exposure of our laboratory personnel was classified as a low risk. Serum samples were stored at –30°C to enable serologic testing for any subsequent illness.

Laboratories in regions where *B. pseudomallei* is not endemic should be aware of misdiagnosis of isolates by automated methods for bacterial identification and antimicrobial drug susceptibility testing. Identification of *Burkholderia* spp. by the Phoenix EpiCenter should be confirmed by molecular methods and by the API 20NE system in suspected cases of *B. pseudomallei* infection. Because of its high rate of accuracy and ease of use, the API 20NE system should be used first for any suspected colony when automated systems do not contain the adequate profile (*10*).

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etymologia

Burkholderia

[burk″hol-dēr′e-ə]

This genus of gram-negative, rod-shaped bacteria comprising animal and plant pathogens was named for American plant pathologist Walter H. Burkholder. Dr. Burkholder first described a particular species of this genus, later called *Burkholderia cepacia* (Latin for "like onion"), after an outbreak of infection in vegetable growers in New York State in 1949. Previously known to cause disease in onion bulbs, these organisms are now recognized as major bacterial lung pathogens in patients with cystic fibrosis. *B. mallei* causes glanders in horses, and *B. pseudomallei* is the etiologic agent of melioidosis in humans and animals. Dr. Burkholder is recognized for helping establish the role of bacteria as plant pathogens.

Source: Dorland's illustrated medical dictionary, 31st edition. Philadelphia: Saunders; 2007; De Soyza A, Silipo A, Lanzetta R, Govan JR, Molinaro A. Chemical and biological features of Burkholderia cepacia complex lipopolysaccarides. Innate Immunity. 2008;14:127.

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HIV Infection among Illegal Migrants, Italy, 2004–2007

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To determine HIV prevalence and place of exposure for illegal migrants in Italy, we tested 3,003 illegal adult migrants for HIV; 29 (0.97%) were HIV positive. Antibody avidity index results (indicators of time of infection) were available for 27 of those persons and showed that 6 (22.2%) presumably acquired their infection after migration.

During the past 2 decades, Italy has had an uncontrolled increase in number of migrants. As many as 4 million (720,000 undocumented) foreign-born persons (≈7% of the population in Italy) are living in Italy (62.5% in the northern region, 25% in the central region, and 12.5% in the southern region) (*1*).

Sexually transmitted infections (STIs) are present in migrants, especially early after migration. Migrants are usually men (single or married) who live alone. Migrant women are often forced into prostitution. These factors may expose them to risky sexual contacts and STIs. Preventive educational campaigns rarely reach migrant communities because of logistic, cultural, and language barriers.

As of December 2008, a total of 60,346 AIDS cases were reported in Italy, where the opt-in strategy (persons need to accept testing) of HIV testing is applied (*2*). The proportion of migrants among persons with cases of AIDS in Italy has progressively increased from 2.5% before 1993 to 20.7% in 2007–2008 (*2*). This finding reflects the increasing number of migrants and their delayed access to screening and medical care (*3*). The proportion of migrants among persons with new cases of HIV infection has also increased from 11% in 1992 to 32% in 2007 in Italy (*2*), a finding that confirms previous data (*4*). Estimated HIV incidence rates among migrants are 64.0 cases (for men) and 52.5 cases (for women)/100,000 persons in 2007. These rates are 11× higher than the HIV incidence rate for native-born Italians (*5*). No reliable information is available on the prevalence of HIV infection in the illegal migrant population in Italy. Data are available only for selected risk groups such as female commercial sex workers (*6*), transsexuals (*7*), and patients with STIs (*8*). Furthermore, no reliable data are available for likely place of infection for persons recently screened and found to be HIV infected. To address these issues, we determined the prevalence and likely place of infection with HIV for an illegal migrant population in Italy.

The Study

The study protocol was reviewed and approved by the ethical boards of all participating centers. The study was conducted during January 2004–December 2007 in clinical centers that offered primary healthcare to illegal migrants in northern (Brescia), central (Rome), and southern (Palermo) Italy. All adult migrants from a non–European Union country who registered for a visit at each center were asked to participate in the study. Participants were divided into 4 groups according to their risk for HIV infection: 1) commercial sex workers, 2) persons reporting unsafe sex (occasional not-for-money homosexual or heterosexual contacts with persons other than their regular partner), 3) persons with other risk factors (intravenous drug use or blood transfusion in their country of origin, and 4) persons with no risk factors identified.

Participants were tested for antibodies against HIV types 1 and 2 and for p24 antigen by using a commercial microparticle enzyme immunoassay (AxSYM HIV Ag/Ab Combo; Abbott Laboratories, Abbott Park, IL, USA). HIV-positive serum samples were further tested for HIV antibody avidity by using the AxSYM HIV 1/2gO assay (Abbott Laboratories) as reported (*9*), to ascertain likely time of infection. An avidity index ≤0.80 indicated that infection was acquired recently (within the past 6 months); a higher index indicated that infection was acquired earlier (>6 months ago). A cutoff value of 0.80 was used and validated as having 93.0% sensitivity, 98.5% specificity (*10*),

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and >90.0% reproducibility. Avidity results were cross-checked with reported time of migration to assess likely place of exposure.

A total of 4,078 persons were invited to participate in the study. Of 3,976 (97.5%) who agreed to participate, 3,003 (73.6%) underwent HIV testing (2,815 in Brescia, 48 in Rome, and 140 in Palermo). In terms of HIV risk for 2,853 respondents, 191 were commercial sex workers, 1,246 practiced unsafe sex, 47 reported other risks, and 1,494 reported no risk factors (total = 2,978 because multiple risk factors were reported by some persons). Demographic characteristics for the participants are shown in Table 1.

HIV-1 infection was detected for 29 (0.97%) of 3,003 participants (95% confidence interval [CI] 0.90%–1.2%); no participants were infected with HIV-2. Avidity index results were obtained for 27 of the 29 HIV-positive participants. Univariate analysis showed that sociodemographic and behavior factors associated with HIV infection were Christian religion (p = 0.029, odds ratio [OR] 3.07, 95% CI 1.06–8.83), migration from sub-Saharan Africa (p = 0.001, OR 11.94, 95% CI 1.61–88.81), commercial sex (p = 0.0001, OR 18.2, 95% CI 6.25–52.97), and unsafe sex (p = 0.016, OR 3.43, 95% CI 1.22–9.66). Multiple logistic regression showed that factors independently associated with increased risk for HIV infection were migration from sub-Saharan Africa (p = 0.0001, OR 3.7, 95% CI 2.2–9.4), commercial sex (p = 0.025, OR 18.4, 95% CI 4.9–48.5), and unsafe sex (p = 0.01, OR 2.3, 95% CI 1.7–8.6).

Place of infection could not be determined for 17 (63.0%) of 27 persons; 6 (22.2%) of 27 were presumably recently infected in Italy, and 4 (14.8%) of 27 presumably acquired their infection in their country of origin before emigration. Results of avidity index determinations are shown in the Figure and Table 2. Sociodemographic characteristics of our population did not differ from those reported nationwide (*1*).

Table 1. Sociodemographic characteristics of 3,003 migrants, Italy, 2004–2007

Characteristic	Value*
Sex	
F	1,587 (52.8)
M	1,416 (47.2)
Median age, y (range)	31 (18–74)
Marital status	
Married	1,236 (43.3)
Single	1,617 (56.7)
Place of origin	
Europe	1,341 (44.7)
Sub-Saharan Africa	674 (22.4)
Asia	470 (15.7)
North America	339 (11.3
Latin America	179 (6.0)
Median migration period, mo (range)	23.4 (0.2–324)
Religion†	
Christianity	1,854 (61.8)
Islam	901 (30.0)
Other	115 (3.8)
None	129 (4.3)
Education, y‡	
≤8	775 (25.9)
>8	2,222 (74.1)
Job status	
Employed	1,545 (51.4)
Unemployed	1,458 (48.6)
Immigration status	
Illegal	2,748 (91.5)
Legal	255 (8.5)

*Except where indicated, values are no. (%).
†n = 2,999.
‡n = 2,997

Conclusions

Our data confirm that many illegal migrants practice unsafe sex (low rate of condom use). These findings are worrisome if one considers poor knowledge of HIV transmission reported in our study population (*11*). Consequently, migrants are particularly vulnerable to STIs, as shown by the high prevalence rate (0.97%) for the adult migrant population, which is higher than the estimated 0.4% prevalence rate for the national population in Italy (*12*). The higher HIV prevalence rate for persons from an area (sub-Saharan Africa) in which HIV is highly endemic might reflect exposure in the country of origin or new infections in the host country. A total of 6 (22.2%) of the 27 HIV infections for which avidity index data were available were probably acquired in Italy by migrants from sub-Saharan Africa (n = 3), eastern Europe (n = 2), and Latin America (n = 1). Conversely, all 4 (14.8%) persons who acquired infection before migration to Italy were originally from sub-Saharan Africa.

Our study had 2 limitations. First, recruitment was not evenly balanced between centers. However, migrants

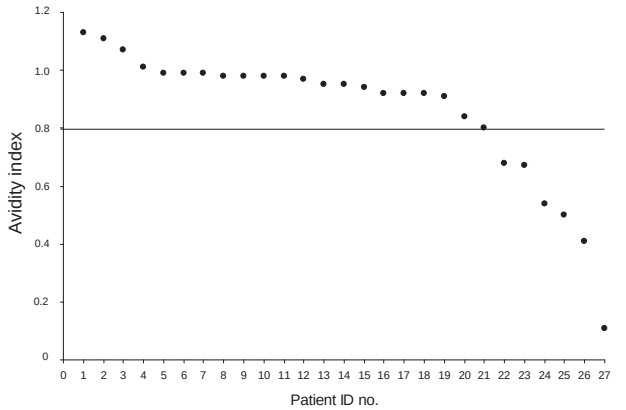

Figure. Antibody avidity indices for 27 HIV-infected migrants, Italy, 2004–2007. Horizontal line indicates the cutoff value. ID, identification.

Table 2. Likely time and place of infection for 27 HIV-infected migrants, Italy, 2004–2007

Time of migration	Antibody avidity index ≤0.8 (infection acquired in past 6 mo), no. (%)	Antibody avidity index >0.8 (infection acquired >6 mo earlier), no. (%)
Past 6 mo	1 (3.7) (place of infection is undetermined)	4 (14.8) (likely place of infection is country of origin)
>6 mo before HIV testing	6 (22.2) (likely place of infection is Italy)	16 (59.3) (place of infection is undetermined)

are unevenly distributed in Italy, with the largest communities in northern Italy. Second, the study acceptance rate was only 73.6%. However, this acceptability rate is similar to rates in other studies in Europe (*13*,*14*). Furthermore, sociodemographic characteristics of our sample were homogeneous with those of other studies from the same centers and nationwide (*1*,*15*), and we did not anticipate any differences between participants and those who did not participate.

Our data show high HIV prevalence for an illegal migrant population in Italy. For persons originally from sub-Saharan Africa and, as for the native population in Italy, practicing commercial or unsafe sex were independently associated with HIV infection. A large proportion of persons had presumably acquired infections after migration. These data indicate the prominent role of social determinants of HIV infection, including marital status and living conditions. Health education and free access to HIV testing and care for the illegal migrant population in western countries is needed, particularly for persons from sub-Saharan Africa.

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Serologic Analysis of Returned Travelers with Fever, Sweden

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We studied 1,432 febrile travelers from Sweden who had returned from malaria-endemic areas during March 2005–March 2008. In 383 patients, paired serum samples were blindly analyzed for influenza and 7 other agents. For 21% of 115 patients with fever of unknown origin, serologic analysis showed that influenza was the major cause.

Many travelers who return from tropical countries have fever of unknown etiology (*1–11*). Earlier studies focusing on fever in returning travelers have used an observation study design with no standardized diagnostics (*1–11*). With the exception of studies generated from the GeoSentinel database (*2,8*), all are single-center studies. In Sweden, guidelines from the National Board of Health and Welfare advise febrile travelers returning from malaria-endemic areas to be examined at departments of infectious diseases. The objective of this multicenter study was to investigate causes of unknown fever by uniformly analyzing paired serum samples.

The Study

The study took place in Sweden from March 14, 2005 through March 14, 2008 at 5 hospitals that had infectious diseases departments. Inclusion criteria were travel within the past 2 months to a malaria-endemic area as defined by the World Health Organization, age ≥18 years, documented temperature ≥38°C at admission or within the previous 2 days, and a decision by the examining clinician to obtain a blood film for suspected malaria.

Participants were identified either through prospective case finding at emergency rooms and outpatient clinics or through retrospective case finding of eligible patients who had not been included in the prospective case finding; these patients were identified through listings of all performed malaria diagnostics. All included patients had been subject to diagnostic investigations (e.g., cultures, serologic analysis, radiographs) on the basis of clinical symptoms and signs as part of routine procedures at each hospital. An infectious diseases specialist at each study site confirmed the diagnosis based on results of investigations performed. The following variables were recorded for all patients: age, gender, travel history (destination, duration, and purpose), diagnosis, and if applicable, days of hospitalization.

Information about pretravel immunizations and time between return to Sweden and onset of symptoms was available only in the group of prospectively included patients. Travel destinations were grouped as Africa, Asia, and America. Purpose of travel was divided into 3 categories: tourism, Swedish residents originating from a malaria-endemic country and visiting friends and relatives in their country of origin, or other.

Paired serum samples from prospectively included patients were blindly analyzed for antibodies to influenza A and B viruses, dengue virus, chikungunya virus, *Brucella* spp., *Leptospira* spp., *Coxiella burnetii*, *Rickettsia* spp., spotted fever group (SFG) rickettsia, and typhus, respectively. If the travel destination was Asia, *Orientia tsutsugamushi* and Japanese encephalitis virus were also analyzed (Figure). A ≥4-fold rise in reciprocal antibody titer against a relevant pathogen was considered a positive result. Comparisons between 2 groups were made by using univariate statistics (χ^2 test); a p value <0.05 was considered significant. The study was approved by the regional Ethics Committee at Karolinska Institute, Stockholm.

In 1,432 febrile travelers, the inclusion criteria were fulfilled. A total of 514 patients were identified through prospective case-finding, and 383 of those agreed to be further tested by using blinded serologic analysis; 918 patients were retrospectively identified. Characteristics of these groups are shown in Table 1. Among the entire group (n = 1,432) before results of additional blinded serologic analysis were obtained, unknown fever was diagnosed in 34%, febrile gastroenteritis in 24%, malaria in 6%, influenza in 3%, and dengue fever in 2.5%. In the 383 prospectively included patients, the diagnosis was unknown fever in 115 (30%); additional serologic analysis established a diagnosis in 24 (21%) of these patients.

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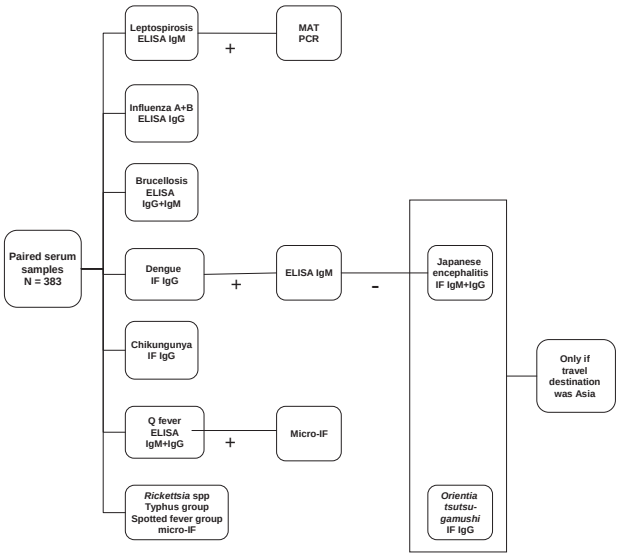

Figure. Flow chart of serologic methods performed blindly on all paired serum samples (n = 383), Sweden. Ig, immunoglobulin; MAT, microscopic agglutination test; IF, immunofluorescent.

The most common diagnosis was influenza (n = 12) followed by SFG rickettsial infection (n = 5), dengue fever (n = 3), leptospirosis (n = 2), Q fever (n = 1), and rickettsial infection caused by *O. tsutsugamushi* (n = 1). A positive serologic result added a co-infection to 23 patients with a diagnosis of illness other than unknown fever; these co-infections were influenza (n = 14), dengue fever (n = 3), typhus group rickettsial infections (n = 2), SFG rickettsial infection (n = 2), leptospirosis (n = 1), and chikungunya fever (n = 1). All infections diagnosed by additional blinded serologic analysis were mild and self-limiting, and the main symptom was fever without typical clinical signs. Fever of unknown etiology was diagnosed in 24% and influenza in 9% of the patients with additional serologic analysis, compared with 35% and 4%, respectively, in the group with routine investigations only (Table 2).

Thirty-six patients in the prospectively included group (n = 514) had influenza diagnosed by both routine examination and additional serologic analysis. Eighteen of the 36 became ill with fever either just before returning to Sweden or within 1 day of arrival, indicating that they acquired the infection abroad; 5 had been home 1–2 days, indicating that the infection could have been acquired either during travel or after the return; and 13 patients had returned from travel >3 days before falling ill with fever, indicating that they most likely became infected in Sweden. Twenty-five of the 36 influenza patients had verified influenza A infection, and 11 had influenza B infection. Nine (25%) patients became ill after returning from a trip occurring well outside the influenza season of the northern hemisphere; 7 had visited Africa, and 2 had traveled to Asia.

Conclusions

Influenza is often missed in routine diagnostics of febrile travelers. Our findings highlight the role of travel in the global spread of influenza and corroborate the findings of influenza in travelers by others (*12*,*13*). Apart from influenza, the most common diseases missed in routine investigations were rickettsial infections, dengue fever, and leptospirosis. Our study adds a new approach by using a systematic collection of paired sera. The retrospective case finding is not fully comparable with the prospective inclusion of patients, and we are missing some retrospective data on type and length of travel. These missing data are, to some extent, compensated by a careful retrospective review of all 918 patients' files, the finding that the characteristics of the 2 groups are similar, and the similarity of the routine investigations for both groups.

Table 1. Characteristics of 1,432 febrile travelers returning from tropical countries, Sweden, March 2005–March 2008*

Characteristics	Patients with routine investigations		Prospectively identified patients with routine investigation + additional serologic analysis, n = 383
	Prospectively identified, n = 131	Retrospectively identified, n = 918	
Median age, y (range)	32 (18–65)	36 (18–84)	37 (18–76)
Median duration of stay, d	20	21†	20
Female gender	56 (43)	420 (46)	162 (42)
Travel to Africa	69 (53)	430 (47)	199 (52)
Travel to Asia	53 (40)	427 (46)	169 (44)
Travel to America	10 (8)	63 (7)	20 (5)
Tourists	76 (58)	581(63)‡	247 (64)
VFR	10 (8), p = 0.05§	126 (14)‡	20 (5), p<0.0001§
Pretravel influenza immunization	8 (6)	NA	53 (14)
Hospitalized after return to Sweden	37 (28)	258 (28)	123 (32)

*Values are no. (%) patients except as indicated. Some travelers visited >1 region, making the percent sum >100%. VFR, visiting friends and relatives (Swedish residents who were born in a malaria-endemic country and who had visited friends and relatives in their country of origin); NA, not applicable.
†In 115 patient files, this information was missing.
‡In 39 patient files, information on type of travel was missing.
§Compared with retrospectively identified patients.

Table 2. Final diagnosis of febrile travelers returning from tropical countries, Sweden, March 2005–March 2008*

Final diagnosis	Additional serologic analysis, n = 383, no. (%) patients	Routine investigations only, n = 1,049, no. (%) patients	p value
Fever of unknown etiology	91 (24)	372 (35)	<0.0001
Influenza	34 (9)	38 (4)	<0.001
Dengue fever	17 (4)	27 (3)	NS
Rickettsial infection	17 (4)	15 (1)	<0.001
Leptospirosis	4 (1)	3 (0.2)	NS
Q fever	3 (0.7)	0	0.004
Chikungunya fever	1	0	NS

*NS, not significant.

Additional blinded serologic analyses were performed by using the same method in the same laboratories. The proportion of final diagnoses with fever of unknown etiology was high compared with that of other studies, even after results of the additional serologic analysis (*1–8,11*). This large proportion of fever with unknown etiology may be explained by the unselected study population in a hospital setting and by a high patient turnover; febrile travelers with a negative malaria film and in good clinical condition are often sent home without extensive investigations or follow up.

To estimate the number of nasopharyngeal swabs taken as a routine test, we retrospectively reviewed a sample of 217 patient files and found that 31 (14%) had been tested for influenza; 6 of those tests yielded positive results. Age, gender ratio, destinations, duration of travel, and hospitalization rates were similar to those of recent studies (*3,7,8*). The finding of undiagnosed rickettsial infections shows that symptoms are often nonspecific, and serologic response often delayed (*14*).

Our results indicate that leptospirosis is an underestimated cause of fever in returned travelers and is not only related to extreme sports (*15*). The relatively low frequency of additional rickettsial infections, dengue, and leptospirosis indicates that paired sera should not be routinely recommended without a specific clinical suspicion. However, this study supports the theory that diseases with classic clinical findings according to text books can also manifest as fever only. Influenza should always, in all seasons, be considered when diagnosing illness in returning febrile travelers.

Acknowledgments

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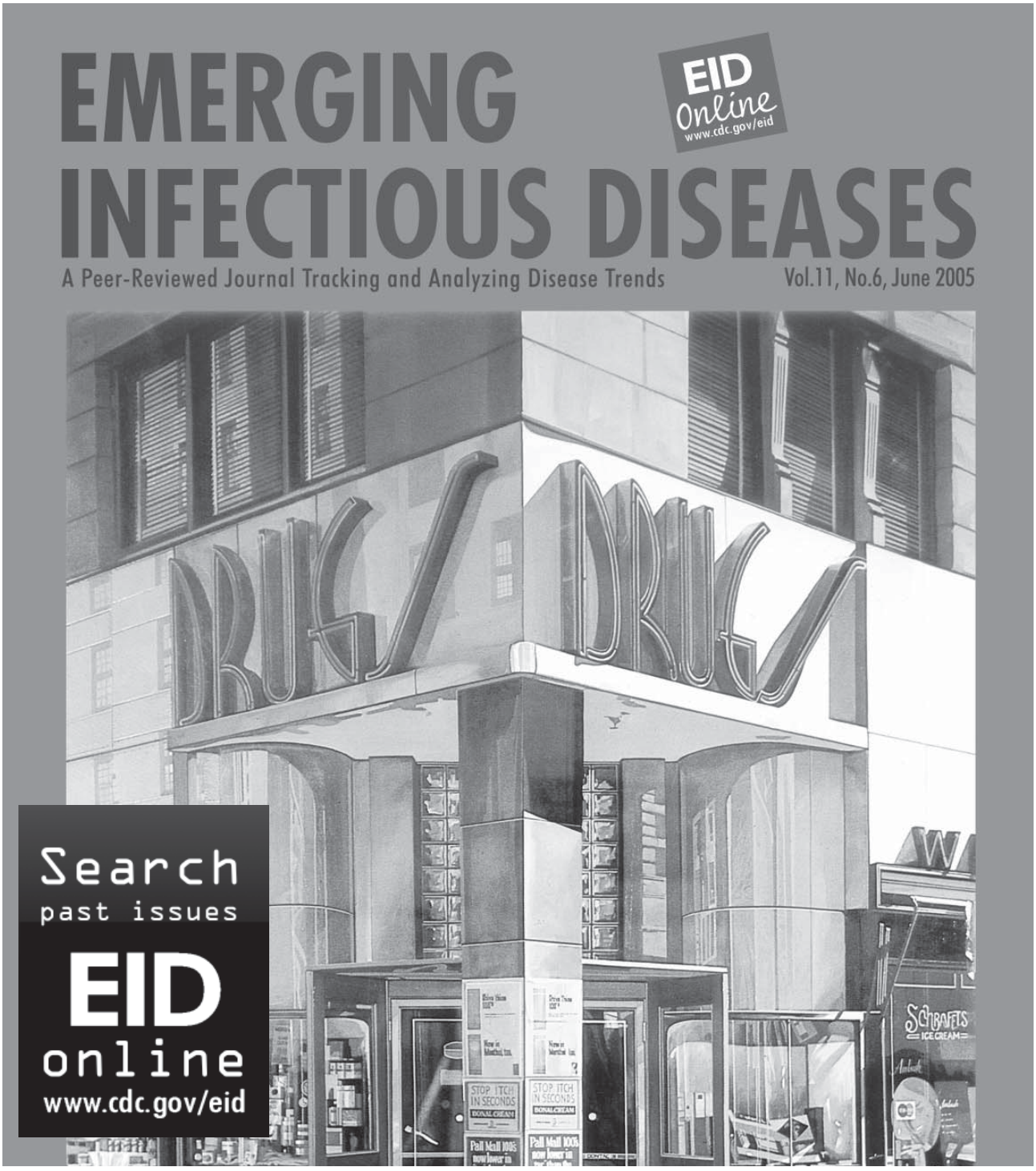

Imported Melioidosis, Israel, 2008

Avivit Cahn, Benjamin Koslowsky, Ran Nir-Paz, Violeta Temper, Nurit Hiller, Alla Karlinsky, Itzhak Gur, Carlos Hidalgo-Grass, Samuel N. Heyman, Allon E. Moses, and Colin Block

In 2008, melioidosis was diagnosed in an agricultural worker from Thailand in the southern Jordan Valley in Israel. He had newly diagnosed diabetes mellitus, fever, multiple abscesses, and osteomyelitis. *Burkholderia pseudomallei* was isolated from urine and blood. Four of 10 laboratory staff members exposed to the organism received chemoprophylaxis, 3 of whom had adverse events.

Melioidosis, which is caused by *Burkholderia pseudomallei*, is endemic to some areas of Southeast Asia and northern Australia (*1*,*2*). Recent data indicate that it is now endemic to most of the Indian subcontinent, southern People's Republic of China, Hong Kong, Taiwan, Papua New Guinea, and other regions (*3*). Most cases reported in other regions were acquired during residence in or travel to disease-endemic regions.

Thailand is a popular destination for backpackers from Israel. Importation of melioidosis has long been anticipated as a potential problem because many persons from Thailand are employed in Israel. Although most infections are asymptomatic (*2*) and usually occur in persons <6 years of age in disease-endemic areas, clinical, often life-threatening, disease most frequently affects adults who have underlying predisposing conditions, especially type 2 diabetes. Incubation period differs according to manner of exposure and size of inoculum and may be short (1 day to 2–3 weeks). However, because the organism has a proclivity for latency (*4*), the disease may appear after months or many years (*2*,*4*). Melioidosis is often manifested as pneumonia, but its hallmark is disseminated abscess formation in viscera, skin, soft tissue, and bone. We report a case of imported melioidosis (*5*) and management and consequences of chemoprophylaxis among laboratory staff exposed to *B. pseudomallei*.

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The Case

A 32-year-old man from Thailand was referred to the emergency department of Hadassah–Hebrew University Hospital at Mount Scopus on July 31, 2008, with newly diagnosed diabetes and fever. He reported 2–3 weeks of fatigue, chills, night sweats, and a weight loss of ≈25 kg in the past 2 months. Two large subcutaneous abscesses had developed over the past several months. The first abscess, in the right axilla, had been drained in May 2008. The second abscess, in the upper right abdominal wall, had been drained in July 2008. Pus was not submitted for culture.

The patient, an agricultural worker, arrived in Israel in November 2007 and was employed at a rural settlement in the southern Jordan Valley. He came from a village in northeastern Thailand where he had worked in rice and sugar cane farming. At the time of admission, he appeared ill and was febrile (39.0°C). Physical examination showed mild cervical lymphadenopathy, nontender hepatomegaly, and healing wounds from the abscess drainage procedures. Laboratory results showed hyperglycemia (glucose level 19.4 mmol/L), normocytic anemia with normal leukocyte and platelet counts, an erythrocyte sedimentation rate of 105 mm/h, and moderately elevated levels of alkaline phosphatase and γ-glutamyl transferase. Kidney function was normal. Urinalysis showed leukocyturia and nitrites. Multiple abscesses were seen in the spleen, lungs, superior pole of the right kidney, prostate gland, and right foot (Figure). A bone scan confirmed osteomyelitis of the right medial malleolus, calcaneus, and first metatarsus.

A diagnosis of melioidosis had been considered from the outset in view of clinical findings of multiple abscesses in a patient with diabetes from a disease-endemic area. A blood culture (BacTec+ Aerobic/F; Becton, Dickinson and Company, Sparks, MD, USA) yielded a nonfermentative, oxidase-positive, motile, colistin-resistant, gram-negative bacilli that showed dry wrinkled colonies. The API 20 NE profile (API; bioMérieux, Durham, NC, USA) was 1556577, which suggested esculin-positive *B. pseudomallei*.

Molecular confirmation was achieved by bidirectional sequencing of a 1.7-kb amplicon specific for the 16S rRNA gene, which was amplified by PCR and primers F229 and R1908 (*6*). Sequencing (National Center for Biotechnology Information accession no. FJ426359) with the same primers showed the known single basepair transition (C/T) at position 75 that distinguishes *B. pseudomallei* from *B. mallei*, the agent of glanders (*6*).

Susceptibility to trimethoprim/sulfamethoxazole was confirmed. MICs were 0.75 mg/L for trimethoprim and 14.25 mg/L for sulfamethoxazole (Etest; AB Biodisk, Solna, Sweden). A urine culture was positive for *B. pseudomallei*, and throat and splenic abscess aspirate cultures were negative.

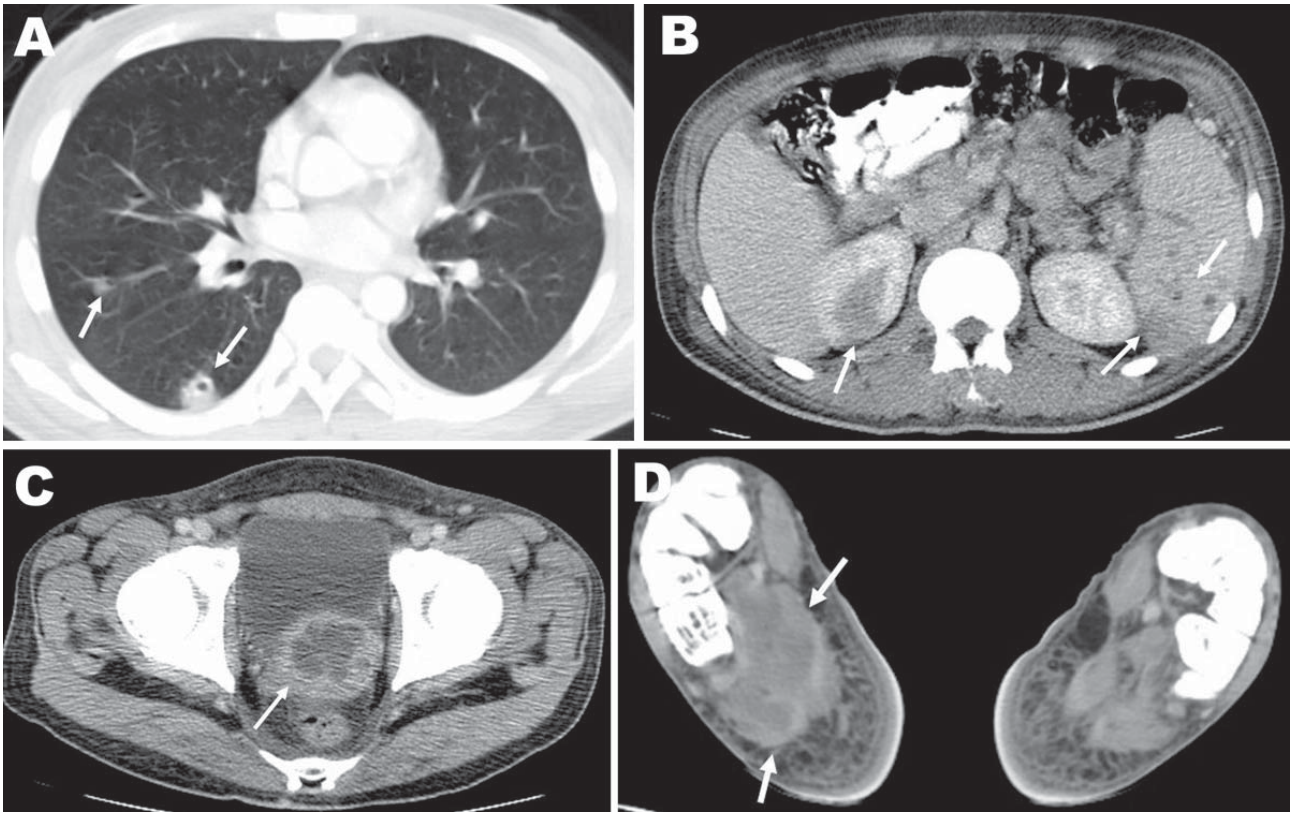

Figure. Computed tomography images showing multiple abscesses in the right lung (A), spleen and upper pole of the right kidney (B), prostate gland (C), and plantar aspect of the right foot (D) (arrows) of the patient.

The patient's first abscess developed ≈6 months after his arrival in Israel, which attests to a long incubation period or prolonged latency after initial asymptomatic infection. New-onset diabetes might have unmasked a preexisting latent infection. He had no history of an illness compatible with melioidosis before he left Thailand.

Treatment with ceftazidime (2 g intravenously 4×/d) and trimethoprim/sulfamethoxazole (1,920 mg orally 2×/d) for 4 weeks resulted in gradual defervescence. The patient was discharged with instructions to take trrimethoprim/sulfamethoxazole (1,920 mg orally 2×/d) and doxycycline (100 mg orally 2×/d) for an additional 20 weeks. He returned to Thailand a few weeks after discharge.

B. pseudomallei infection has been regarded as an occupational hazard for clinical microbiologists (*7*–*9*). Although risk for laboratory-acquired infection is relatively low (*7*), the nature of the disease demands special precautions in dealing with its causative organism. With recent designation of *B. pseudomallei* as a select agent by the Centers for Disease Control and Prevention (www.cdc.gov/od/sap), it has been proposed that Biosafety Level 2 practices, which were advised for clinical diagnostic work (*10*), be replaced by stricter safety practices (*11*).

Accordingly, a risk assessment was performed, and 4 persons who had handled the cultures outside a biologic safety cabinet were offered postexposure chemoprophylaxis with trimethoprim/sulfamethoxazole (1,920 mg orally every 8 h) for 3 weeks) (*11*). The frequency of rashes was worrisome: rashes developed in 2 persons (1 elected to complete the course of doxycycline [100 mg orally 2×/d for 3 weeks] and 1 stopped treatment after 10 days). One person was so uncomfortable that she refused further treatment on day 12. Only 1 person completed the course of trimethoprim/sulfamethoxazole without adverse effects. Symptoms consistent with melioidosis did not develop in any of the exposed staff. Serum samples from 10 staff members who had had any contact with the cultures were collected within 2–3 days of exposure and after 6–8 weeks and tested by using an indirect hemagglutination test at Mahidol University in Bangkok. All serologic test results were negative, an outcome consistent with findings of a published report (*8*).

Conclusions

Many workers (10,600 in 2007) from Thailand have been employed in agriculture in Israel (*12*). Cases of melioidosis may not have been detected until the present pa-

tient because routine preemployment medical screenings may have excluded persons with the disease from entry into Israel or unfamiliarity with the disease led to underdiagnosis.

Migration of populations requires awareness regarding unforeseen diseases, as recently highlighted in a clinical problem-solving exercise (*13*). If one considers the abscesses in our patient, melioidosis would have likely been diagnosed earlier had this patient remained in Thailand. In any case, if the routine practice of culturing pus from his abscesses had been followed, the diagnosis might have been made earlier. This finding is a reminder to physicians that they should adhere to basic clinical guidelines. Conversely, clinical evidence and close cooperation of ward physicians, the infectious disease service, and the laboratory staff likely expedited identification of the organism.

The diagnosis of melioidosis in a region where this disease is not endemic depends on physician awareness and laboratory capability. In the patient reported here, clinical suspicion, suggested by multiple visceral abscesses, preceded microbiologic confirmation, which was expedited by internists and the infectious disease service. Clinical microbiology laboratories worldwide should prepare for dealing with *B. pseudomallei* and include it in the workup of unusual nonfermentative, colistin-resistant, gram-negative bacilli, particularly in workers from Thailand or other melioidosis-endemic countries. The issue of chemoprophylaxis for persons with laboratory exposures, and its potential for adverse events, requires careful immediate decision making, especially if one considers the rarity of this albeit disabling disease among laboratory staff.

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Wealth Inequality and Tuberculosis Elimination in Europe

Jonathan E. Suk, Davide Manissero, Guido Büscher, and Jan C. Semenza

In Europe, wealth inequality is directly related to tuberculosis (TB) notification (R^2 = 0.69), while in countries with lower TB rates, higher proportions of TB cases occur in foreign-born persons. Particularly during times of financial upheaval, efforts to eliminate TB must address social inequality.

The current global financial crisis may be expected to exacerbate health inequalities (*1*), which in turn lead to differential health outcomes (*2*,*3*). In Europe, for example, discrepancies between those living in lower and higher socioeconomic positions are manifested through differential death rates from chronic diseases, such as cardiovascular and cerebrovascular diseases, as well as alcohol- and smoking-related diseases (*4*).

Similar discrepancies also exist for communicable diseases. A comprehensive literature review demonstrated that in every European Union (EU) member state, vulnerable groups (those with low educational or income levels, migrants, persons engaged in high-risk lifestyles) have a disproportionately higher incidence of communicable diseases (*5*). However, because the overall effect of communicable diseases is currently estimated to be 9% of total diseases in Europe, such differences are difficult to quantify (*6*). Furthermore, surveillance systems do not systematically capture indicators of socioeconomic status (such as education, occupation, ethnicity, or housing tenure) or link those indicators to specific persons.

Tuberculosis (TB) provides a good case study for further analyzing correlations between communicable diseases and wealth distribution. Historically, the decline of TB incidence in Europe preceded the advent of anti-TB drugs and coincided with rapid improvement of quality of life (*7*). Whether this link continues to be valid for high-income countries remains an open question. Earlier studies carried out after the resurgence of TB in the late 1980s in North America and in Europe indicated that, along with HIV infection and drug resistance, socioeconomic factors were a major determinant in acquiring TB (*8*,*9*). The 27 EU member states, with a wide distribution of TB notification rates (4–138/100,000 population/year) as well as diverse levels of wealth as measured by gross domestic product (GDP) in purchasing power standards (PPS) per capita (8,600–63,100) (Eurostat; http://epp.eurostat.ec.europa.eu), represent an optimal setting in which to analyze whether a correlation can be detected between wealth, social cohesion, and TB.

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The Study

In this ecologic study, distribution of TB prevalence rates (all forms, per 100,000 population per year, 2006) (*10*) for each EU member state was plotted against 2 measures of income distribution to examine the most descriptive indicator of how socioeconomic setting relates to TB prevalence in Europe: 1) the Gini coefficient, a common measure of inequality of income distribution within a country (*11*); and 2) Eurostat's inequality of income distribution ratio, which measures the ratio of total income received by the 20% of the population with the highest income (top quintile) to that received by the 20% of the population with the lowest income (lowest quintile). The Gini coefficient was not strongly associated with TB prevalence in Europe (R^2 = 0.22), nor was Eurostat's inequality of income distribution ratio (R^2 = 0.34).

Hypothesizing that the quantification of a country's wealth (i.e., GDP), along with its distribution, would correlate better than either indicator separately, we computed an indicator called the public wealth index (PWI). This index divides a nation's economic wealth (using Eurostat data on GDP in PPS per capita) by its level of social cohesion (using the Eurostat inequality of income distribution ratio). Effectively, this metric takes the relative high level of wealth in Europe into account while also controlling for its distribution. It favors wealthy countries with low ratios of income inequality: the top 5 scores on the public wealth index were generated by Luxembourg, Norway, Denmark, Sweden, and the Netherlands.

Using the PWI, we then developed a simple regression model to explain TB prevalence rates. Because of the structure of the data, we used a log-log transformation in R version 2.8 (*12*). The explanatory variable (PWI) and the dependent variable (TB prevalence rates), were log-transformed. We analyzed all 27 EU member states as well as Norway and Iceland. The model yielded a strong inverse relationship between PWI and TB rates with a correlation coefficient of R^2 = 0.69. The differences when using the estimator for the intercept parameter in the model (14.36, $p<0.001$) and when using the estimated regression parameter for the logarithmic PWI (–1.39, $p<0.001$) were both

significant. The observed values and the regression line with no log transformation are shown in the Figure.

Finally, to demonstrate the differences in the composition of TB populations between countries, we plotted the percentage of foreign-born TB case-patients within a country (a surveillance proxy for immigrant populations, which is typically defined as place of birth, except in Austria, Belgium, Bulgaria, Malta, and Poland, where it is defined as place of citizenship as reported in 2006) (*10*). As countries rank higher on the PWI, the proportion of TB case-patients that are foreign-born generally increased (Figure). With increasing PWI status, TB rates dropped, but the proportion of foreign-born TB case-patients increased.

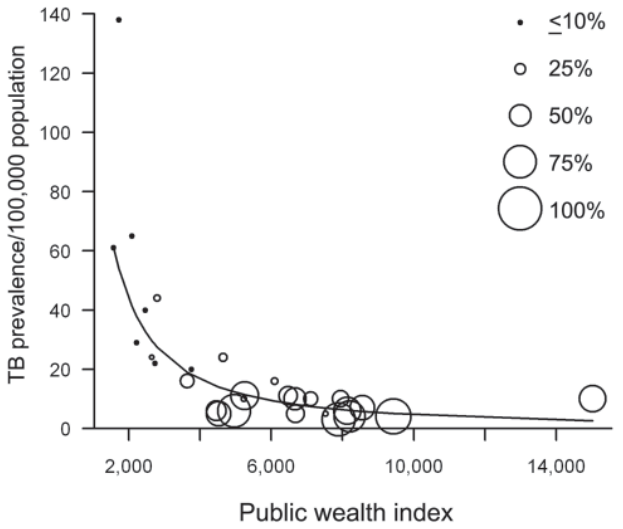

Figure. Public wealth index and tuberculosis (TB) prevalence rates in the 27 European Union member states plus Norway and Iceland, 2006.

Conclusions

We demonstrate a strong inverse relationship between PWI scores and TB rates. The data presented here are, however, subject to important limitations. First, aggregation bias is inherent in all ecologic studies, which are not able to disaggregate individual level risk factors important in TB transmission. Second, national-level surveillance information consists of few socioeconomic indicators. One of the indicators, foreign born, is perhaps an unfortunate proxy term for migrant populations, but it is the only one available. The term is further limiting because definitions of foreign born vary between countries, as discussed earlier. Third, inconsistencies in TB reporting likely occur across the European Union, although this would in any case bias the results away from the null hypothesis.

Nevertheless, given the strong correlation between the PWI and TB rates across Europe, as well as the strong trend linking high PWI with higher rates of TB among foreign-born populations, our data lend support to the notion of ensuring equality, both within and between nations, as an important building block for effective TB control. Yet, as the Figure suggests, especially for countries with higher scores on the PWI, emphasis must also be placed on directly engaging specific vulnerable groups for public health action, whether these groups consist of foreign-born persons, HIV-positive persons, Roma people (http://web.worldbank.org/WBSITE/EXTERNAL/COUNTRIES/ECAEXT/EXTROMA/0,,contentMDK:20341647~menuPK:648308~pagePK:64168445~piPK:64168309~theSitePK:615987,00.html), or others.

The current financial crisis could exacerbate the conditions of existing vulnerable groups as well as create new ones. For example, the EU Directorate for Employment, Social Affairs and Equal Opportunities estimates that 16% of Europe's population currently lives below the poverty line (*13*). Rising unemployment rates could push this rate even higher, with implications for factors that drive TB spread such as the quality of housing and sanitation. Returning jobless migrants might also be particularly vulnerable if they are no longer able to access their country's social insurance systems. Thus, particularly for countries with high incidences of TB, advancing social equalities is fully compatible with the aim of lowering TB prevalence rates. Indeed, addressing social and environmental determinants (such as social inclusion, education and training, crowding, and indoor air pollution) could pay dividends in the fight against TB during difficult economic times.

Data related to the financial crisis and its effects on public health will need to be carefully scrutinized as they become available. In the meantime, the public health community must continue to both defend and act upon the insights from the World Health Organization Commission on the Social Determinants of Health, which has so eloquently inserted discussion of social inequalities into public health discourse (*3*). Addressing TB among vulnerable populations and tailoring services to these groups (*14)* will also be an essential component of any strategy aiming at progressing towards TB elimination, as the action plan by the European Centre for Disease Prevention and Control suggests (*15*).

Mr Suk currently works at the European Centre for Disease Prevention and Control in the Scientific Advice Unit's Section on Future Threats and Determinants. He has a background in the social sciences and biology, and his research focuses on social determinants of infectious diseases.

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Dengue Virus Serotype 4, Northeastern Peru, 2008

Brett M. Forshey, Amy C. Morrison, Cristhopher Cruz, Claudio Rocha, Stalin Vilcarromero, Carolina Guevara, Daria E. Camacho, Araceli Alava, César Madrid, Luis Beingolea, Víctor Suarez, Guillermo Comach, and Tadeusz J. Kochel

In 2008, dengue virus serotype 4 (DENV-4) emerged in northeastern Peru, causing a large outbreak and displacing DENV-3, which had predominated for the previous 6 years. Phylogenetic analysis of 2008 and 2009 isolates support their inclusion into DENV-4 genotype II, forming a lineage distinct from strains that had previously circulated in the region.

Infection by any 1 of 4 distinct dengue virus serotypes (DENV-1 through DENV-4) can result in disease manifestations ranging from asymptomatic or mild to severe outcomes, including dengue hemorrhagic fever (DHF) and dengue shock syndrome. Several lines of evidence point toward secondary infection by a heterologous serotype as one of the critical risk factors for DHF (*1*), underscoring the need to monitor circulating DENV serotypes and genotypes.

In Latin America, >30 countries and regions have reported DENV circulation, totaling >900,000 dengue fever cases, 26,000 DHF cases, and 300 deaths in 2007 (*2*). Following the breakdown of a hemisphere-wide *Aedes aegypti* mosquito eradication campaign conducted in the mid-20th century, vector populations expanded and all 4 DENV serotypes reemerged or were reintroduced into the Western Hemisphere. Outbreaks of DENV-2 and DENV-3 were first detected in the 1960s, followed by the introduction of DENV-1 in 1977 and DENV-4 in 1981 (*3,4*).

Since its introduction into the Americas in 1981, DENV-4 has circulated continuously in the Caribbean basin (*5*) and northern South America with little evidence of widespread transmission further south into the continent during the past 25 years (*4,6,7*). We report the emergence of DENV-4 strains belonging to genotype II in the tropical rainforest and coastal regions of northern Peru, replacing DENV-3 subtype III (*8*) as the predominant strain in the region.

The Study

Patients with acute, undifferentiated, febrile illness were recruited into a clinic-based surveillance study conducted jointly by the US Naval Medical Research Center Detachment (NMRCD) and the Peruvian and Ecuadorian Institutes of Health (Figure 1). Study protocols (NMRCD.2000.0006

Figure 1. Map of study sites in Ecuador, Peru, and Venezuela. The study in Peru and Ecuador was operated jointly by the US Naval Medical Research Center Detachment with each country's Institutes of Health. Samples from Venezuela were collected in and around Maracay through the Aragua State Epidemiologic Surveillance Program from patients with suspected dengue virus (DENV) infection. Cities denoted by filled circles indicate study sites where DENV serotype 4 strains were isolated, whereas open circles denote active study sites where no DENV–4 circulation was detected during the course of the study.

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DOI: 10.3201/eid1511.090663

[Peru] and NMRCD.2001.0002 [Ecuador]) were approved by the Naval Medical Research Center Institutional Review Boards in compliance with all US federal regulations governing the protection of human subjects.

Patient sera were injected onto African green monkey Vero cells or *Ae. albopictus* C6/36 cells and examined for a range of arboviruses, including all 4 DENV serotypes, by immunofluorescent assay. From 2000 through 2008, DENV-3 (1,572 isolates) was the dominant serotype in circulation in the study sites, followed by DENV-1 (205 isolates) and DENV-2 (87 isolates). From the initiation of the study in May 2000 until February 2006, DENV-4 circulation was rarely detected in the NMRCD-affiliated study sites in either country; the exceptions were a small number of isolates in 2000 in Tumbes, Peru (n = 2) and Guyaquil, Ecuador (n = 6).

Low-level DENV-4 transmission was again detected in Ecuador and coastal Peru during 2006 and 2007, in isolates from patients in Tumbes, Trujillo, and Guayaquil, none of whom had reported recent history of travel outside their respective areas. DENV-4 continued to circulate in sites along the northern coast of Peru in 2008 and 2009, in co-circulation with DENV-1. In February 2008, DENV-4 spread to the cities of Iquitos and Yurimaguas, located in the Loreto Department in the tropical rainforest region of northeastern Peru. By October 2008, DENV-4 had nearly completely displaced DENV-3, which had been the only serotype detected in the region during the previous 3 years. Nine (56%) of 16 DENV isolates obtained from febrile patients in August 2008, 55 (85%) of 65 isolates obtained in September 2008, and 305 (98%) of 311 isolates obtained from October 2008 through February 2009 were DENV-4. After the introduction of DENV-4, the total number of DENV-3 isolates decreased during peak months of DENV transmission (October through February) from 176 during 2006–2007 and 420 during 2007–2008 to <10 isolates during the same period in 2008–2009. More recently (March 2009), DENV-4 strains have spread south to Lima, the capital city of Peru, causing a small, localized outbreak on a military base.

To characterize the DENV-4 isolates, a 1,485-bp sequence covering the entire mature envelope (E) gene was amplified and sequenced from a representative set of viruses from Guayaquil (n = 6), Tumbes (n = 6), Piura (n = 2), Trujillo (n = 1), Iquitos (n = 9), Yurimaguas (n = 7), and Lima (n = 2), all collected during 2000 through 2009. Isolates collected in Peru since 2006 shared >99.5% nucleotide identity but exhibited <97% identity with DENV-4 strains collected in Ecuador and coastal Peru in 2000. At the amino acid level, the 2006–2009 isolates were nearly invariant, with ≤1 amino acid difference.

For further characterization, the DENV-4 strains from Ecuador and Peru were compared with DENV-4 sequences from Latin America (*9*,*10*) and Southeast Asia (*11*) available from the GenBank database. In addition, to provide a wider array of recent isolates from the Caribbean region, DENV-4 isolated from febrile patients in Aragua State, Venezuela (n = 15) collected during 2000 through 2007 were sequenced. Based on phylogenetic analyses, all DENV-4 isolates belong to genotype II (data not shown), although the 2006–2009 isolates segregated into a markedly different clade than the strains from 2000 (Figure 2). The 2000 isolates clustered more closely with a previous 1994 Ecuador isolate (*9*), related to the initial 1981 Caribbean introduction DENV-4 strains (designated as subtype A). The 2006–2009 isolates were most closely related to recent DENV-4 isolates from Venezuela, with as low as 0.8% nucleotide divergence, and formed a lineage

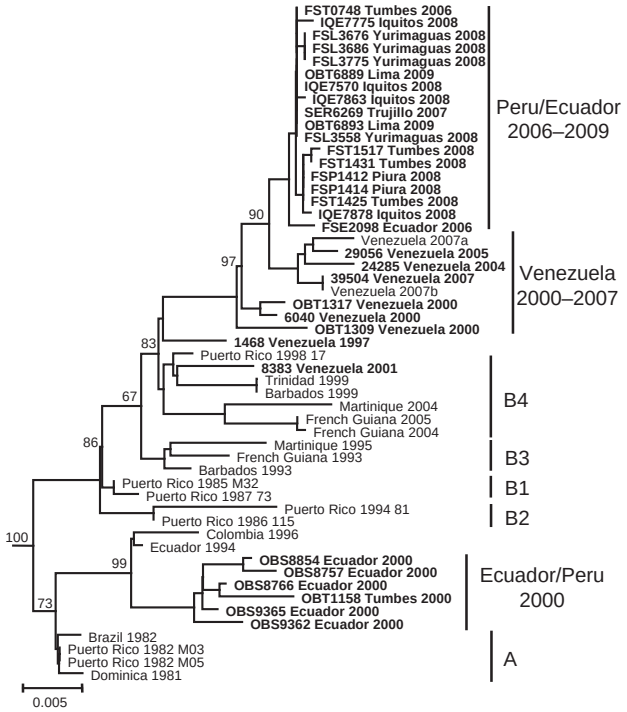

Figure 2. Phylogenetic analysis of the envelope gene of dengue virus serotype 4 (DENV–4) strains from Ecuador, Peru, and Venezuela. Similar topologies were observed from neighbor-joining (depicted), maximum likelihood, and maximum parsimony analyses, implemented in PAUP* v.4.0b10 (*12*). The general time reversible model of evolution was used for neighbor-joining and maximum-likelihood analyses. DENV-4 genotype I strains (not shown) were included as an outgroup. Bootstrap values (based on 1,000 replicates) >65 are shown at major nodes. Isolates first reported in this study are shown in **boldface** and with sample identification code. Some sequenced isolates from Peru and Venezuela that share high nucleotide identity (>99.7%) with depicted strains were omitted to reduce redundancy and improve clarity of the figure. Sequences were deposited in the GenBank database under the accession nos. GQ139572–GQ139577 (Ecuador), GQ139547–GQ139571 (Peru), and GQ139578–GQ139591 (Venezuela). Scale bar indicates number of nucleotide substitutions per site.

distinct from previously published DENV-4 Caribbean basin strains (*9*,*10*), with strong bootstrap support (Figure 2). This lineage is distinguished from previously reported DENV-4 genotype II strains by 3 conserved amino acid variations in the E protein: S64L, A235T, and S403A.

Conclusions

We report DENV-4 expanding rapidly through northern Peru, particularly in the Loreto Department in the tropical rainforest region, spreading through a population immunologically naïve to this serotype. In the past 2 decades, populations in northern Peru have been exposed to the other 3 DENV serotypes, thus increasing the possibility for severe disease, including DHF. In Iquitos, DHF was first reported during a DENV-3 epidemic in 2004 (M. Sihuincha and C. Rocha, pers. comm.). DHF had not been observed after the introduction of DENV-2 despite large numbers of infected residents (*13*), presumably due to cross-protection afforded by prior infection with DENV-1 (*14*). For the currently circulating lineage of DENV-4, the levels of either cross-protection or antibody-dependent enhancement of infection resulting from prior heterologous infection remain to be determined.

The mechanisms responsible for DENV-3 displacement in Loreto are unclear. Following several years of DENV-3 circulation in the region, serotype-specific antibody prevalence is high (≈45% of the population, based on virus neutralization assays [T.J. Kochel, unpub. data]). However, it is unlikely that herd immunity is sufficient to explain the dramatic decrease in DENV-3 transmission. The presence of broadly cross-protective antibodies during the acute and early convalescent phases following DENV-4 infection, when combined with the large number of DENV-3 immune persons, could suppress transmission of DENV-3 strains (*15*). Another possibility is serotype competition within the vector species. Analysis of virus strains from *Ae. aegypti* mosquitoes collected during the transitional period could help elucidate whether such intertypic competition is occurring.

Genetically, the 2006–2009 isolates analyzed in this study do not appear to be related to viruses collected from Ecuador and northern Peru during 2000, which were similar to the initial Latin American introduction strains (Figure 2). Instead the 2006–2009 isolates were most closely related to viruses from Venezuela collected during 2000 through 2007, forming a lineage distinct from the DENV-4 genotype II B4 lineage (*10*). Genetic conservation among isolates from Peru and similarity with isolates from Venezuela support an introduction event into northern Peru and Ecuador from the northern region of South America before 2006, and a subsequent introduction from coastal Peru into Loreto, although more data from other regions of South America and the Caribbean basin would be necessary to more clearly delineate the geographic spread of this virus strain.

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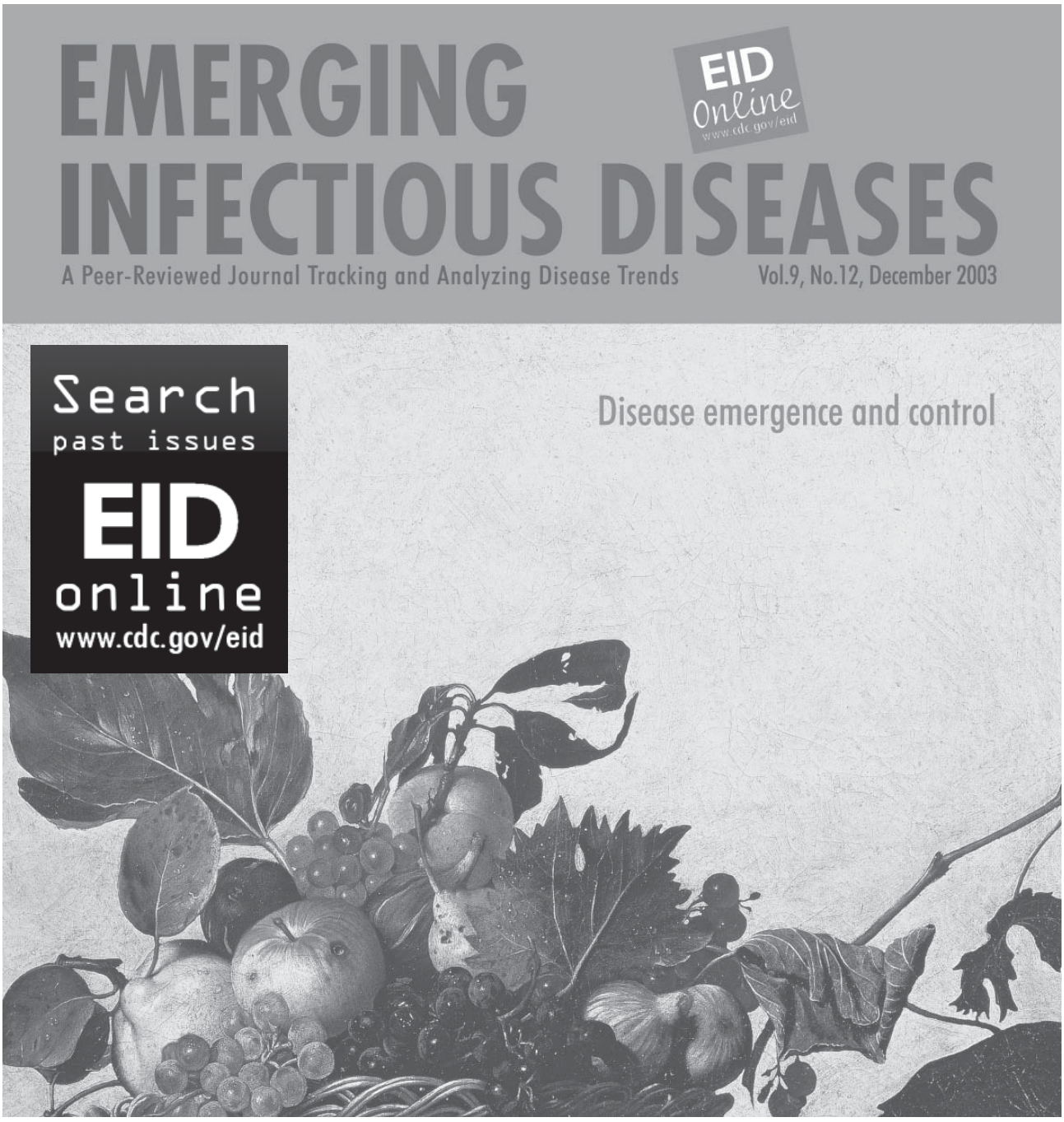

Hepatitis C Seroprevalence and Associated Risk Factors, Anyang, China

Fangfang Liu,[1] Ke Chen,[1] Zhonghu He, Tao Ning, Yaqi Pan, Hong Cai, and Yang Ke

Hepatitis C virus screening was conducted among 8,226 residents 25–65 years of age in 4 counties of China; virus prevalence was 0.9%. A subsequent case–control study indicated blood transfusion (odds ratio [OR] 4.55), esophageal balloon examination (OR 3.78), and intravenous injection (OR 5.83) were associated with infection.

Hepatitis C virus (HCV) infection shows clear differences in prevalence among geographic regions, according to World Health Organization data (*1*). HCV prevalence also varies over time and with behavioral changes (*2*,*3*). HCV prevalence in the People's Republic of China nationwide was estimated at 3.2% in a 1992 survey (*4*), but studies have reported regional prevalence rates ranging from 0% to 31.9% (*5*–*7*). In developing countries, transmission of HCV typically results primarily from iatrogenic factors, such as blood transfusion and inadequate sterilization or reuse of medical equipment (*8*), but in industrialized countries, risk resulting from these factors has been greatly reduced (*9*,*10*).

In an esophageal endoscopic survey (2006–2008) in Anyang, Henan Province, China, blood screening for the HCV antibody was carried out in all participants. Because HCV infection is an important public health issue, a case–control study was performed among HCV-positive case-patients with matched controls to evaluate risk factors for HCV infection in the area where the esophageal endoscopic survey was conducted.

The Study

An endoscopic survey (2006–2008) for esophageal cancer was conducted in 8 villages of 4 counties of Anyang, Henan Province, China (Figure). The villages were selected on the basis of population size, location, and village administrative capabilities. A total of 10,240 permanent residents were eligible for the survey; 8,226 (80.3%) persons 25–65 years of age (median age 42.0, M:F sex ratio 1.00:1.18) without cardiovascular or psychological diseases were interviewed and had blood drawn. A total of 74 participants were seropositive for HCV in this screening; 69 of them were enrolled in the subsequent case–control study. Each seropositive person was matched with 3 negative controls randomly selected from seronegative participants (2.5%) of the same village, gender, and age (±2 years). A questionnaire regarding lifetime risk factors for HCV infection was given to HCV seropositive case-patients and matched controls. The Institutional Review Board of the School of Oncology, Peking University, China, approved this study. Informed consent was obtained from all participants.

Serum samples were separated from blood samples by centrifugation and tested for HCV in the Anyang Cancer Hospital for case-patients from Anyang, Lin, and Tangyin counties, and in the Hua County Hospital for case-patients from Hua County. ELISAs were performed to evaluate for HCV antibody (Diagnostic Kit for HCV ELISA 3.0; Auto-Bio Co., Zhengzhou, China). HCV-positive case-patients submitted an additional blood sample for a confirmatory HCV test in Anyang Cancer Hospital. Positivity for HCV antibody in these 2 tests was independently confirmed at Beijing Friendship Hospital by ELISA (Diagnostic Kit HCV 3.0; Abbott GmbH & Co. KG, Wiesbaden-Delkenheim, Germany). We determined the positive predictive value of the anti-HCV tests conducted in China to be 98.3% by using the testing result of the Abbott diagnostic kit as a standard. Assays were monitored with internal and external quality controls.

We examined group differences using the χ^2 test. Univariate and multivariate conditional logistic regression were used to identify significant factors for HCV infection. Data entry and statistical analysis were conducted using Epi Data 3.1 (www.cdc.gov/epiinfo) and SAS 9.1.3 (SAS, Cary, NC, USA); $p<0.05$ was considered significant.

Seventy-four (0.9%) of 8,266 participants were HCV positive. Prevalence of infection varied significantly with age ($p<0.001$) and county of origin ($p<0.001$) but not with gender (Table 1). HCV prevalence was significantly higher in participants >50 years of age. Prevalence was highest in Lin County (2.8%), followed by Anyang County (0.7%), Tangyin County (0.4%), and Hua County (0.2%) (Table 1). The Lin County >50-year-old group showed an 18.25-fold higher risk for HCV infection (95% confidence interval [CI] 9.29–35.83) when compared with non–Lin County participants ≤50 years of age (data not shown).

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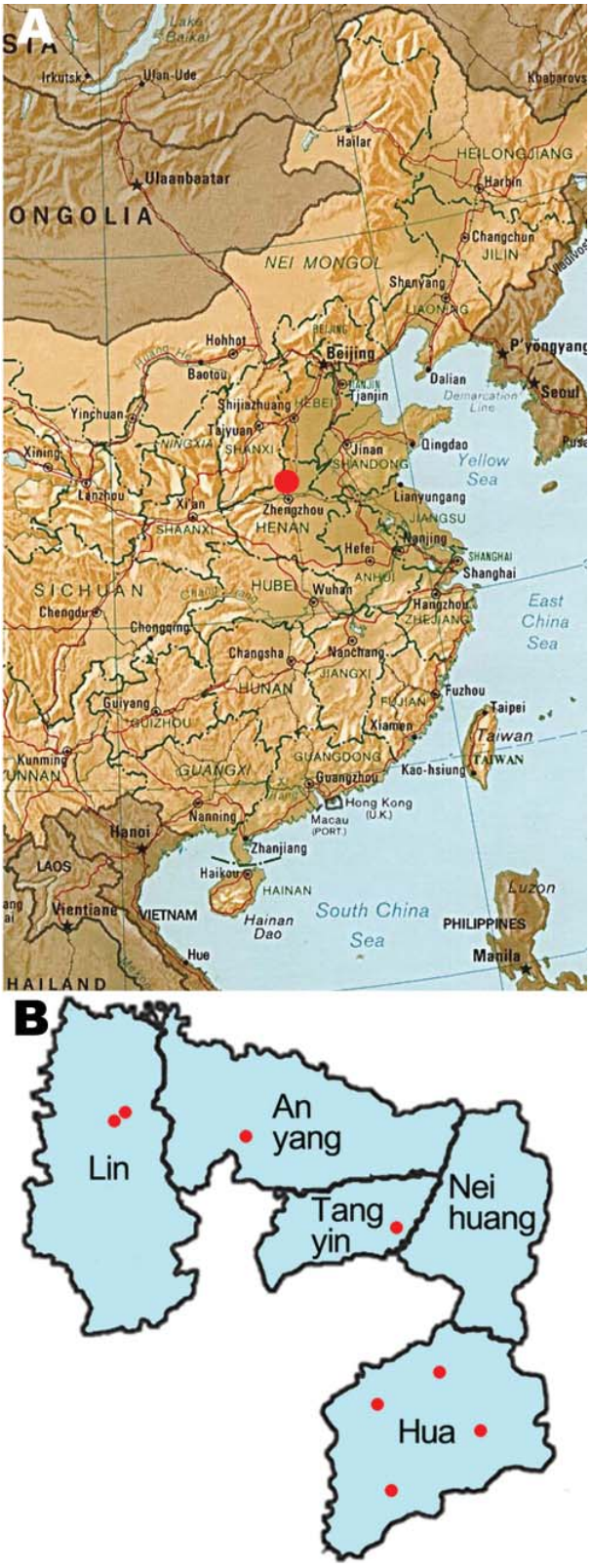

Figure. A) Map of eastern China showing the location of Anyang (red dot). B) Villages (red dots) targeted in the 2006–2008 hepatitis C virus prevalence study.

Univariate conditional logistic regression was used to evaluate possible risk factors based on information collected from the 69 HCV-positive participants and 207 matched controls. Transfusion with blood and blood products, intravenous injection, and procedures including Caesarean section, acupuncture, gastroscopy, and esophageal balloon examination were associated with higher risk for HCV infection. No instances of hemodialysis, organ transplantation, drug use, or homosexual behavior were identified. However, when these risk factors were analyzed in a multivariate model, only blood transfusion (odds ratio [OR] 4.55, 95% CI 1.34–15.42), intravenous injection (OR 5.83, 95% CI 2.66–12.80), and esophageal balloon examination (OR 3.78, 95% CI 1.32–10.79) were significant (Table 2). A repeat analysis of participants from Lin County produced almost identical results (data not shown).

Conclusions

In this 2006–2008 study, overall HCV prevalence was 0.9%, with prevalence highest in the ≥50-year-old group of Lin County (4.7%). In a 2000 study of 55- to 84-year-old Lin County residents, the prevalence of HCV was 9.6% (*7*). Several possible reasons could explain these differences. One is that the average age in the previous study (range 64–84 years) was greater than that in our study (range 25–65 years); older persons were more likely to be infected in both the previous study and our study. The time interval between these 2 studies might also have contributed to the change in HCV prevalence.

A case–control study was performed to identify HCV infection risk factors. Blood transfusion and medical intravenous injection with reusable glass syringes and needles, which are established HCV risk factors, were associated with HCV infection (*10*,*11*). In addition, esophageal balloon examination, a less commonly identified route of HCV infection, also increased the risk for HCV infection. In the recent past (1980–2000), esophageal balloon examination, which was designed for early cytologic detection

Table 1. Demographic distribution and HCV infection status of participants (n = 8,226) in an esophageal endoscopic survey for HCV, Anyang, China, 2006–2008*

Variable	Total no. (%)	HCV-positive, no. (%)	p value
Age, y			
≤50	5,766 (70.1)	37 (0.6)	<0.001
>50	2,460 (29.9)	37 (1.5)	
Sex			
M	3,782 (46.0)	31 (0.8)	0.479
F	4,444 (54.0)	43 (1.0)	
County			
Hua	4,022 (48.9)	7 (0.2)	<0.001
Anyang	838 (10.2)	6 (0.7)	
Lin	1,980 (24.1)	55 (2.8)	
Tangyin	1,386 (16.8)	6 (0.4)	

*HCV, hepatitis C virus.

Table 2. Conditional logistic analysis of risk factors associated with hepatitis C virus infection, Anyang, China, 2006–2008*

Risk factor†	Response	Total no.	HCV negative, no. (%)	HCV positive, no. (%)	OR (95% CI)	Adjusted OR (95% CI)
Alcohol consumption	No	258	195 (94.2)	63 (91.3)	1	
	Yes	18	12 (5.8)	6 (8.7)	1.71 (0.54–5.39)	
Blood donation	No	261	199 (96.1)	62 (89.9)	1	
	Yes	15	8 (3.9)	7 (10.1)	3 (0.99–9.09)	
Blood transfusion	No	248	197 (95.2)	51 (73.9)	1	1
	Yes	28	10 (4.8)	18 (26.1)	6.32‡ (2.73–14.6)	4.55§ (1.34–15.42)
Blood products transfusion	No	249	191 (92.3)	58 (84.1)	1	1
	Yes	27	16 (7.7)	11 (15.9)	2.49§ (1.03–6.05)	0.99 (0.28–3.5)
Intramuscular injection	No	39	32 (15.5)	7 (10.1)	1	
	Yes	237	175 (84.5)	62 (89.9)	1.77 (0.69–4.59)	
Intravenous injection	No	153	136 (65.7)	17 (24.6)	1	1
	Yes	123	71 (34.3)	52 (75.4)	6.75‡ (3.41–13.36)	5.83‡ (2.66–12.8)
Visited a dentist	No	136	103 (49.8)	33 (47.8)	1	
	Yes	140	104 (50.2)	36 (52.2)	1.09 (0.62–1.9)	
Had surgery	No	210	171 (82.6)	39 (56.5)	1	1
	Yes	66	36 (17.4)	30 (43.5)	3.78‡ (2.01–7.1)	2.29 (0.92–5.71)
Shared nail clippers	No	66	51 (24.6)	15 (21.7)	1	
	Yes	210	156 (75.4)	54 (78.3)	1.17 (0.62–2.23)	
No. sexual partners	1	262	194 (93.7)	68 (98.6)	1	
	>1	14	13 (6.3)	1 (1.4)	0.21 (0.03–1.66)	
Pierced ears	No	173	129 (62.3)	44 (63.8)	1	
	Yes	103	78 (37.7)	25 (36.2)	0.88 (0.4–1.96)	
Acupuncture	No	215	168 (81.2)	47 (68.1)	1	
	Yes	61	39 (18.8)	22 (31.9)	2.15§ (1.11–4.13)	1.61 (0.69–3.76)
Gastroscopy	No	246	190 (91.8)	56 (81.2)	1	
	Yes	30	17 (8.2)	13 (18.8)	2.92§ (1.27–6.72)	2.06 (0.63–6.7)
Esophageal balloon examination	No	240	190 (91.8)	50 (72.5)	1	
	Yes	36	17 (8.2)	19 (27.5)	5.95‡ (2.44–14.5)	3.78§ (1.32–10.79)

*HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval.
†Blood transfusion, blood products transfusion, intravenous injection, operation, acupuncture, gastroscopy, and esophageal balloon examination were included in the multivariate model.
‡p<0.01.
§p<0.05.

of esophageal lesions, was relatively common in China for diagnosis and screening of persons in high-risk populations (*12*). In this technique, the patient swallows a balloon covered with a cotton net. The balloon is inflated within the patient's stomach. Exfoliated esophageal cells are then scraped off the mucosa by pulling out the balloon. Bleeding of esophageal mucosa can occur. The balloon and cotton net were designed to be nonreusable. Nonetheless, on some occasions, balloons were reused after manual cleaning. This technique is no longer widely used; however, Lin County is a high-risk area for esophageal cancer. Screening for esophageal cancer using balloon examination was performed in this region before 2000. Reuse of balloons and occasional bleeding during the procedure may have caused transmission of HCV in this population.

A nationwide survey for HCV infection in China was performed in 1992; prevalence was 3.1% for residents in rural areas. However, prevalence of viral infection was not consistent across regional populations, similar to what was observed in the present study (*4*). On the basis of these regional differences in HCV distribution and the potential risk factors identified in this study, we strongly suggest that unregulated medical procedures may confer substantial risk for HCV spread.

Chronic infection will develop in ≈75%–85% of persons infected with HCV, and cirrhosis of the liver will develop in up to 20% of chronically infected persons. Hepatocellular carcinoma will develop in ≈3%–4% of patients with HCV-associated cirrhosis each year (*13–15*). Given the serious social and economic effect of this HCV epidemic, strengthening administrative regulation of medical practice, especially in rural areas, and providing appropriate education to the public about HCV infection and its transmission should be given higher priority in public health policy.

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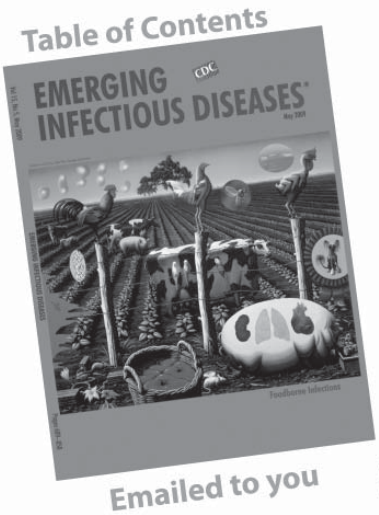

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Travel-related Schistosomiasis Acquired in Laos

Eyal Leshem, Eyal Meltzer, Esther Marva, and Eli Schwartz

Twelve Israeli travelers acquired schistosomiasis in Laos during 2002–2008, and 7 of them had acute schistosomiasis. The patients were probably exposed to *Schistosoma mekongi* in southern Laos, an area known to be endemic for schistosomiasis. Four possibly were infected in northern Laos, where reports of schistosomiasis are rare.

Schistosomiasis is a widely distributed intravascular trematode infection. Estimates indicate that >200 million people are infected with schistosomiasis, mainly in Africa. In Asia, 3 *Schistosoma* species cause human infection: *S. japonicum*, *S. malayensis*, *and S. mekongi*. *S. mekongi* endemicity is thought to be limited to a 200-km area of the Mekong River Basin, stretching from the southern tip of Laos to Cambodia (Figure) (*1*). However, this parasite's intermediary host, freshwater snails (*Neotricula aperta*), has recently been found to be more widespread and to be advancing northwards (*1*,*2*). Attwood has suggested that *S. mekongi* may extend as far north as Khammouane Province in southern Laos (Figure) (*1*,*3*).

Acute schistosomiasis is a transient hypersensitivity reaction associated with tissue migration of *Schistosoma* spp. larvae in nonimmune persons. This syndrome is characterized by fever, cough, fatigue, myalgia, urticaria, and gastrointestinal complaints. Although acute schistosmiasis caused by *S. japonicum* was extensively studied long ago (*4*), we found no reports of acute schistosmiasis caused by *S. mekongi*. Moreover, current literature states that acute schistosmiasis has never been described as a feature of *S. mekongi* infection (*5*).

The Study

The study was conducted at the Center for Geographic Medicine at Sheba Medical Center and was approved by the institutional review board. Travel-related schistosomiasis was defined as a case of schistosomiasis confirmed by serology or ova detection in a traveler who had been exposed to freshwater in Laos. Travelers were thoroughly questioned regarding freshwater exposures during the index trip and any previous trips to schistosomiasis-endemic areas.

Serologic diagnosis conducted at the Israel Ministry of Health (MOH) Central Laboratories in Jerusalem was based on the soluble egg antigen ELISA test (IVD Research Inc., Carlsbad, CA, USA), a nonspecies-specific method. Consequently, most samples (11/12) were sent to the US Centers for Disease Control and Prevention (CDC) for species-specific serologic assays (Falcon Assay Screening Test ELISA [FAST-ELISA], CDC, Atlanta, GA, USA) (*6*). This method is used for *S. japonicum* serodiagnosis; specific serology for *S. mekongi* is unavailable.

Stool specimens were tested for the presence of *Schistosoma* spp. ova (merthiolate–iodine-formaldehyde technique) at the Israel MOH and Clalit Health Services laboratories. Fisher exact test was used for categoric data and the Student *t* test for continuous data. Statistical significance was set at $p<0.05$.

During 2002–2008, 12 patients (5 male, 7 female [2 children]) had travel-related schistosomiasis acquired in Laos (Table 1). No freshwater exposures in *Schistosoma*-endemic areas in Asia (excluding the index trip to Laos) were reported by patients (Table 1).

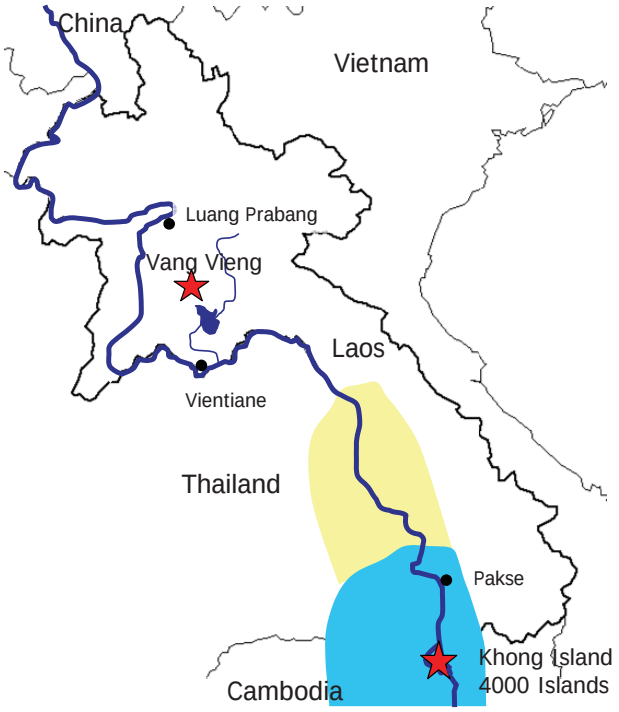

Figure. Map of Laos. The area in which *Schistosoma mekongi* is known to be endemic is highlighted in light blue. The area highlighted in light yellow shows both the known area and the area predicted by Attwood's paleogeographic models (*1*) to be inhabited by *Neotricula aperta* (freshwater snails), the known intermediary host for *S. mekongi*. Two foci of travel-related schistosomiasis are also highlighted with red stars. The dark blue line shows the route of the Mekong River.

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Table 1. Demographic, epidemiologic, and clinical characteristics of travelers with schistosomiasis acquired in Laos*

Patient no.	Age, y/sex	Clinical features	Countries visited during index trip	Places of water exposure in Laos	Date of exposure	Date of clinic visit	Possible past exposure to schistosomiasis	Serology, genus-specific/ immunoblot	Stool ova
1	27/F	AS	China, Laos, Cambodia, Thailand	4,000 Islands	2003 Apr	2003 Sep	1997, Malawi	Pos/*S. japonicum*	Neg
2	22/F	AS	Thailand, Laos, Cambodia, Vietnam	Vang Vieng, 4,000 Islands	2007 Jun	2007 Aug	No	Pos/*S. japonicum*	Neg
3	23/M	AS	Thailand, Nepal, Laos, Vietnam, Cambodia	Vang Vieng, 4,000 Islands	2006 Apr	2006 Jun	No	Pos/*S. japonicum*	ND
4	38/F	AS	India, Thailand, Laos, Cambodia	Vang Vieng, 4,000 Islands	2008 Apr	2008 May	No	Pos/*S. japonicum*	Neg
5	9/F	AS	India, Thailand, Laos, Cambodia	Vang Vieng, 4,000 Islands	2008 Apr	2008 May	No	Pos/*S. japonicum*	Pos
6	42/M	AS	India, Thailand, Laos, Cambodia	Vang Vieng, 4,000 Islands	2008 Apr	2008 May	No	Pos/*S. japonicum*	ND
7	6/M	AS	India, Thailand, Laos, Cambodia	Vang Vieng, 4,000 Islands	2008 Apr	2008 May	No	Pos/*S. japonicum*	ND
8	24/F	CS	Thailand, Laos, India	Vang Vieng, 4000 Islands	2003 Nov	2006 May	No	Pos/Neg	Neg
9	36/F	CS	India, Thailand, Vietnam, Cambodia, Laos	Vang Vieng	2004 Mar	2005 May	No	Pos/*S. japonicum*	ND
10	26/F	CS	Thailand, Laos, Australia, New Zealand	Vang Vieng	2003 Nov	2004 Nov	No	Pos/*S. haematobium*†	Neg
11	22/M	CS	Thailand, Laos, China, Nepal	Vang Vieng	2007 Feb	2007 Dec	No	Pos/ND	Neg
12	23/M	CDA	Thailand, Laos, Vietnam, Cambodia, China	Vang Vieng	2007 Mar	2007 Aug	No	Pos/*S. japonicum*	ND

*AS, acute schistosomiasis; CS, chronic schistosomiasis; pos, positive; neg, negative; ND, not done; S. *japonicum, Schistosoma japonicum*; *S. hematobium*, *Schistosoma haematobium*; CDA, cercarial dermatitis, asymptomatic.
†Patient tested positive on *S. haematobium* immunoblot.

Mean patient age was 24 years (range, 6–42 years). Seven patients were exposed to freshwater in both southern and northern Laos (4,000 Islands and the town of Vang Vieng, respectively); 1 patient was exposed only in southern Laos (Figure). Notably, 4 patients reported freshwater exposure exclusively in northern Laos (Vang Vieng). Three of the 4 reported no travel in southern Laos; 1 patient (Table 1, patient 10) visited southern Laos but was not exposed to freshwater. Exposure occurred during the months of February–April for 9 of the 12 patients.

Seven patients had a diagnosis of acute schistosmiasis. Fever (86%), headache (86%), urticarial rash (71%), and cough (71%) were the most prevalent acute schistosmiasis symptoms (Table 2). Four patients reported chronic gastrointestinal symptoms (abdominal pain and discomfort, diarrhea or loose stools). One patient described a pruritic papular rash that appeared hours after exposure and resolved within a few days (suspected cercarial dermatitis). The patient was asymptomatic upon evaluation at our clinic (Table 1, patient 12).

Diagnosis was made by positive serology in all 12 patients. Eleven serum samples were sent to CDC for speciation; 9 patients had positive immunoblots for *S. japonicum* (Table 1). One patient had a positive immunoblot for *S. haematobium*; this result was judged to be a cross-reaction because the patient had never visited *S. haematobium*–endemic areas.

S. mekongi/japonicum ova were detected in stool samples of 1 of 7 patients who submitted such samples for ova detection (Table 1). Issues of technical proficiency and expertise precluded a definite conclusion regarding speciation according to egg size. Laboratory findings in 5 patients with acute schistosmiasis were significant for marked eosinophilia (Table 2).

All infected patients were treated with praziquantel at ≥12 weeks postexposure to avoid treatment failure (*8*). Of the acute schistosmiasis patients, 3 of the 7 required corticosteroid treatment during the acute illness.

Conclusions

Acute schistosmiasis, which is considered to be a hypersensitivity reaction that usually develops a few weeks after *Schistosoma* infection, is best studied in nonimmune travelers rather than in continuously exposed local popula-

Table 2. Clinical characteristics of patients with acute schistosomiasis acquired in Laos compared with those of case-patients from Tanzania*

Clinical characteristic	Infections acquired in Laos, n = 7	Infections among case-patients in Tanzania, n = 19
Fever	6 (86)	13 (68)
Headache	6 (86)†	2 (10)
Urticaria	5 (71)	7 (37)
Cough	5 (71)	15 (78)
Fatigue	4 (57)	11 (58)
Angioedema	3 (42)	2 (10)
Abdominal pain	3 (42)	5 (26)
Diarrhea	2 (28)	7 (37)
Myalgia	2 (28)	7 (37)
Cercarial dermatitis	1 (14)	3 (16)
Time from exposure to seeking medical care, d (±SD)	27 (±4)	38 (±22)
Eosinophil count, cells/mm (±SD)	3,595 (±3,218)	3,535 (±2,394)

*Patients with cases suspected to be caused by *Schistosoma mekongi* infection compared with patients infected with *S. mansoni* and/or *S. haematobium* in Tanzania (*7*). All values are no. (%) except as indicated.
†p<0.001.

tions. We report 7 cases of acute schistosmiasis presumably caused by *S. mekongi* infection acquired in Laos. Acute schistosmiasis is reportedly not a species-specific phenomenon but may develop after infection with any *Schistosoma* spp. (*8*), a view strengthened by this report.

Symptoms of acute schistosmiasis caused by *S. mekongi*, although a small number of cases, appear similar to symptoms of acute schistosmiasis caused by *S. mansoni* or *S. haematobium* (*7*) (Table 2). The only symptom significantly more prevalent in acute schistosmiasis caused by *S. mekongi* was headache.

Most *Schistosoma* infections in travelers are acquired in Africa (*8*,*9*). In our clinic, travel-related schistosomiasis acquired outside Africa was diagnosed only in travelers exposed in Laos (*8*). This exposure is probably due to the popularity of water-related adventure activities among travelers to Laos.

S. mekongi–endemic areas in Laos have presumably included only the southern reaches of the Mekong River (Figure) (*1*,*2*,*5*). However, this assumption may reflect a serendipitous effect because schistosomiasis in Laos was first diagnosed in immigrants originating from this region. These early schistosomiasis cases led early epidemiologic surveys to the region of Khong, where most subsequent studies were performed (*5*,*10*). Since these epidemiologic surveys were conducted, *S. mekongi* infections acquired in northern Laos have been described only anecdotally (*11*–*13*).

In this report, we describe 4 patients with schistosomiasis apparently acquired in northern Laos (Figure) after exposure to freshwater exclusively in Vang Vieng; that is, they reported no other freshwater exposure during their visit to Laos. However, because of lack of species-specific serology and the inability to find *Schistosoma* ova in these patients' stool samples, we can not determine which *Schistosoma* spp. caused their infection.

Most of these patients were infected during February–April, Mekong's early low-water period, indicating a seasonal infection pattern similar to that of local populations (*5*). The increased risk of schistosomiasis during the late dry season should be conveyed to travelers during pretravel consultations.

Our observation of *Schistosoma* infection in the 4 travelers exposed exclusively in Vang Vieng has several limitations. First, the diagnosis was based on positive serology and not on ova detection. Cross-reactivity of nonhuman *Schistosoma* spp. with *S. japonicum* in serologic studies (e.g., *S. sinensium* or *S. ovuncatum*) could have caused seropositivity in our patients. Second, these 4 travelers (Table 1, patients 9–12) have visited other areas in Asia known to be *Schistosoma* endemic (China) or suspected to be (Vietnam, Nepal). Although travelers were thoroughly questioned regarding possible freshwater exposures, they may not have recalled minor exposures. Finally, we found no published malacologic surveys of the Vang Vieng area, and most experts regard this area as free from *N. aperta*, the intermediate host of *S. mekongi*.

In other world regions (e.g., Lake Malawi in Africa), *Schistosoma*-infected travelers have served as sentinels alerting local authorities to previously unsuspected foci of transmission (*14*). The cases of schistosomiasis in travelers thought to be exposed only in northern Laos, an area where dam building may have changed local conditions, mandates a systematic revaluation of *S. mekongi* distribution in Laos.

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Buruli Ulcer in United Kingdom Tourist Returning from Latin America

Hugh McGann, Pieter Stragier, Françoise Portaels, Deborah Gascoyne-Binzi, Timothy Collyns, Sebastian Lucas, and Damian Mawer

We report a case of Buruli ulcer in a tourist from the United Kingdom. The disease was almost certainly acquired in Brazil, where only 1 case had previously been reported. The delay in diagnosis highlights the need for physicians to be aware of the disease and its epidemiology.

Buruli ulcer (BU) is caused by infection with *Mycobacterium ulcerans* and can lead to extensive destruction of skin and soft tissue (*1*). The disease is endemic in >30 tropical and subtropical countries worldwide (*2*,*3*). It is associated with exposure to stagnant water or slow-flowing rivers. Most cases occur in Africa, and only 1 case has been previously reported from Brazil (*4*). It has rarely been described in travelers returning from an endemic area (*5*,*6*). We report a case of a UK tourist with *M. ulcerans* infection after a trip to Brazil and other parts of Latin America.

The Case

The travel itinerary for this 27-year-old man, his history of water exposure, and the clinical progression of the lesion all support the hypothesis that he acquired the infection in the Pantanal region of southern Brazil. He spent 4 days there starting on August 11, 2007, and participated in trekking on horseback through wetlands and a canoe trip during which he was immersed in water on several occasions. From that region, he flew to the Bolivian cities of Santa Cruz and La Paz, before traveling overland to Lake Titicaca. After 3 days there, he journeyed on to Arequipa, Peru. On September 2, he took a bus trip to the Colca Canyon. During this journey, 17 days after leaving the Pantanal, he first noticed a small, painless papule with an overlying scab on the lateral aspect of his left knee. He had no history of trauma or insect bite and no further water exposure after leaving Brazil.

He then visited Cuzco and some surrounding sites for a week, before entering the rainforests of Manu National Park for a 3-day visit on September 14. Here his leg was immersed in stagnant water on several occasions, although the papular lesion was well established and enlarging by this time. From Cuzco, he went to Lima, the capital of Peru, where he arrived on September 27. When examined in a local clinic 1 week later, the lesion was described as a 1-cm, painless ulcer. Over the next 6 weeks, it gradually increased in size during his travels through Ecuador.

He returned to the UK on November, 15, 2007, and attended the dermatology department of his local hospital. The ulcer was debrided with larval therapy and measured 11 × 6 cm (Figure 1, panel A). A skin biopsy was performed, and multiple acid-fast bacilli (AFB) were seen on microscopy. Histologic analysis showed necrosis of the subcutaneous fat and deep dermal tissue with clusters of AFB but no granuloma formation (Figure 2). Tissue samples were also sent for mycobacterial culture, but results were negative after 12 weeks incubation. The patient was treated with clarithromycin for presumed *M. marinum* infection.

Despite this therapy, the ulcer continued to enlarge, reaching 16 × 10 cm with deeply undermined edges and necrosis of the surrounding skin (Figure 1, panel B). In January 2008, he was referred to the Infection and Travel Medicine Department at our hospital in Leeds. BU was suspected clinically. A swab taken from beneath the ulcer edge was positive for AFB on direct microscopy. A sample was sent to the Institute of Tropical Medicine in Antwerp,

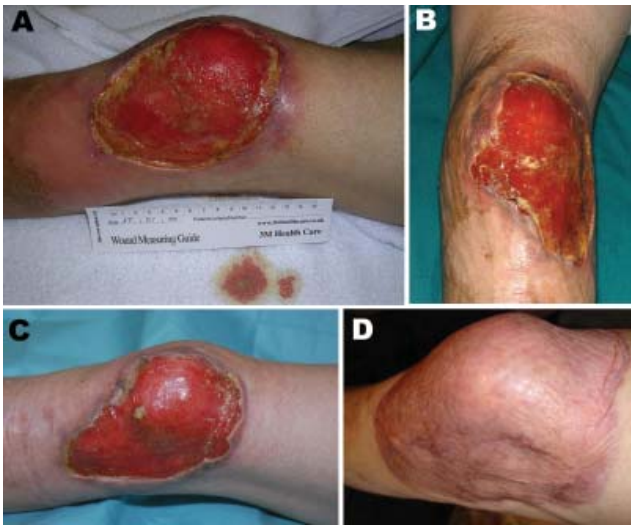

Figure 1. Progression of Buruli ulcer adjacent to the left knee of United Kingdom tourist after returning from Latin America. A) November 2007, on patient's return to the United Kingdom; B) January 2008, before *Mycobacterium ulcerans* therapy; C) April 2008, after 12 weeks of antimicrobial drug therapy; D) January 2009, 9 months after split-skin grafting.

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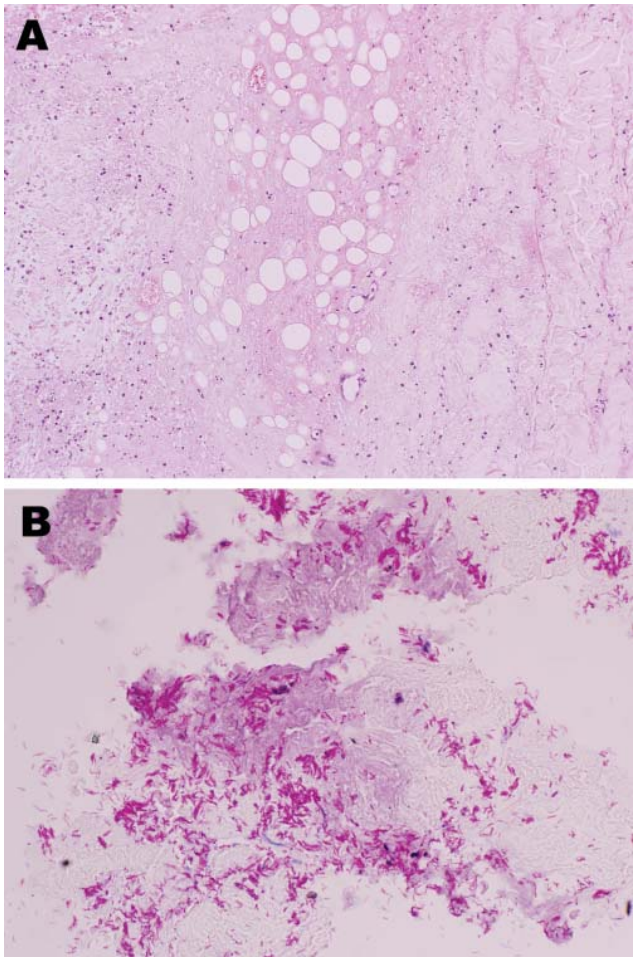

Figure 2. Histologic analysis showing necrosis of subcutaneous fat and deep dermal tissue of the patient. A) Noninflammatory infarction-like necrosis related to cytopathic effect of the mycolactone toxin secreted by *Mycobacterium ulcerans*. B) Abundant mycobacteria within the necrosis.

Belgium for PCR testing for *M. ulcerans* by detection of the insertion sequence *2404* (IS*2404*), which was positive. Further prolonged cultures for AFB were negative in both the United Kingdom and Belgium.

Because of the extensive nature of the ulcer, the patient was treated for 12 weeks with a daily regimen of 600 mg of oral rifampicin and 400 mg of moxifloxacin. Intravenous amikacin, 15 mg/kg once a day, was added during the first 8 weeks. Response to antimicrobial treatment was satisfactory: the ulcer reduced to 12 × 10 cm, the edges were no longer undermined, and the surrounding skin appeared healthy (Figure 1, panel C). To accelerate healing, split skin grafting was performed 1 month after completion of antimicrobial drug therapy. Nine months later, complete healing had occurred (Figure 1, panel D).

The clinical diagnosis of BU is usually straightforward once the disease has been considered. However, diagnosis may be delayed, as in this case, when the patient is in a country in which BU is not endemic, especially when exposure has occurred in a region where the disease is not well recognized. A major diagnostic advance has been the development of PCR for insertion sequence *2404*, one of 2 multicopy insertion sequences in the *M. ulcerans* genome (*7*). The technique, usually performed on tissue biopsy samples, can also be performed directly from ulcer swabs (*8*) and has a sensitivity and specificity of ≈100% (*9*). It is theoretically a rapid test but is not routinely available in many countries, including those where BU is endemic.

Conclusions

Data from the World Health Organization indicate that the greatest number of BU cases occur in western Africa (*2*). Cases have been reported from the Western Hemisphere, although apart from French Guiana, the disease is considered rare in Central or South America (*3*). For example, in Peru during 1969–2007, only 11 cases were documented (*10*). BU may be endemic in Brazil, but, to our knowledge, only 1 case has been previously reported from this country (*4*).

The use of mycobacterial-interspersed repetitive-unit variable number of tandem repeat typing (MIRU-VNTR) has made it possible to distinguish between different strains of *M. ulcerans* (*11*). Most countries outside Africa have their own unique MIRU-VNTR profile(s). The profile of this patient's isolate was determined as 10112N, identical to that recovered from a patient from Tumbes in northwest Peru (*10*). This previous case could indicate that our patient acquired his infection in Peru. The epidemiologic evidence, however, supports the hypothesis that it was acquired in the Pantanal region of Brazil, suggesting that this MIRU-VNTR profile has a geographic distribution wider than originally thought.

Cases of BU diagnosed in countries where the disease is not endemic are rare. To our knowledge, only 21 such cases have been reported (*12*). These cases may occur either in a migrant from a country endemic for BU, where the disease is acquired in the country of origin, or in a traveler from a country where BU is not endemic, as in this case. This BU case appears to be only the second reported in a traveler returning from the Western Hemisphere (*12*). Physicians should be aware of its features because early diagnosis and treatment help prevent long-term disability that may result from this infection. Cases such as this one, reported from countries where BU is rare, serve as a reminder that the disease is probably endemic to a larger area than is usually considered.

Dr McGann is a consultant physician and specialist in infectious diseases at St. James's University Hospital, Leeds, UK. His research interest is caring for patients with community, nosocomial, and travel-related infections.

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Mayaro Fever Virus, Brazilian Amazon

Raimunda S.S. Azevedo, Eliana V.P. Silva, Valéria L. Carvalho, Sueli G. Rodrigues, Joaquim P. Nunes Neto, Hamilton A.O. Monteiro, Victor S. Peixoto, Jannifer O. Chiang, Márcio R.T. Nunes, and Pedro F.C. Vasconcelos

In February 2008, a Mayaro fever virus (MAYV) outbreak occurred in a settlement in Santa Barbara municipality, northern Brazil. Patients had rash, fever, and severe arthralgia lasting up to 7 days. Immunoglobulin M against MAYV was detected by ELISA in 36 persons; 3 MAYV isolates sequenced were characterized as genotype D.

Mayaro virus (MAYV) is a member of the family *Togaviridae* and the genus *Alphavirus*. Recent molecular studies have recognized 2 MAYV lineages: genotypes D and L (*1*). MAYV has been associated with a dengue-like illness with rash, fever, and severe arthralgia in tropical South America. Arthralgia lasts for several weeks and affects principally ankles, wrists, and toes, but also can affect major joints. MAYV causes a mild to moderately severe acute febrile illness of 3–5 days' duration with uneventful recovery (*2*).

The Study

In February 2008, an outbreak of a dengue-like illness was reported in the Pau D'arco settlement, 38 km from Belém, Para state, in the Brazilian Amazon (online Appendix Figure, available from www.cdc.gov/EID/content/15/11/1830-appF.htm). This rural community has 48 houses with ≈150 inhabitants, many of whom live in poor conditions. They reside in the middle of a native forest, in softwood houses, in the municipality of Santa Barbara (2007 population ≈14,439).

A total of 105 persons were examined in a house-to-house survey. They reported a febrile illness within the past 30 days, had a current febrile illness, or reported contact with persons with febrile illness. Fifty-three resided in the settlement (50 were agricultural workers), and 52 were agronomy students at a public university in Belém and had been training for a week at a field station adjacent to the settlement. The students slept in the station for a week; their activities included periodic visits to the settlement and sporadic ingression to the forest. Students and agricultural workers were bled weekly by convenience from March 17 through April 4, 2008. All serum samples were processed by ELISA for detection of immunoglobulin (Ig) M (*3*).

During the same diurnal period (9:00 AM–3:00 PM), mosquitoes were captured in the settlement by using human bait on the ground and in the forest canopy (≈15 m high) near the residences. A total of 832 (49 lots) *Culicidae* mosquitoes were collected and frozen before being used for virus isolation. Of these, 188 (11 lots) were *Haemagogus janthinomys*, the main vector of MAYV; the remaining 644 (38 lots) were mainly members of the genera *Wyeomyia, Aedes, Sabethes*, and *Limatus*.

Newborn mice (*Mus musculus*) and C6/36 cells were inoculated with acute-phase serum from samples collected from febrile patients and pooled mosquitoes, as previously described (*4*,*5*). The inoculated animals and cells were observed daily, and the presence of virus was confirmed by complement fixation and immunofluorescent assays (*4*). Three MAYV strains were isolated: 2 from febrile persons and 1 from a pool with 2 *H. janthinomys* mosquitoes collected at ground level. All 3 strains were isolated with both assays.

IgM was detected in 36 (34%) serum samples (Figure 1, panel A). Of those 36 samples, 23 (64%) were collected from residents of the settlement, and 13 (36%) were from residents of Belém and Ananindeua municipalities; these persons had visited the settlement area for a week (Figure 2, panel B). Persons with Mayaro fever ranged in age from 4 to 55 years, and 21 (58%) were male (Figure 1, panel C). Fifty-two percent of MAYV-positive persons were students, 31% were agriculturists, and 17% participated in other activities (Figure 1, panel D).

Of the 36 MAYV-infected persons, 33 were symptomatic. Illness was characterized by sudden onset of fever (100% of patients), arthralgia (89%), myalgia (75%), headache (64%), articular edema (58%), rash (49%), and retroocular pain (44%). Other less frequent symptoms were itching (33%), dizziness (25%), anorexia (22%), swollen lymph nodes (17%), and vomiting (4%).

Other common exanthematic illnesses in Brazil included in the differential diagnoses were dengue fever, rubella, B19 parvovirus, human herpesvirus 6, infectious mononucleosis, malaria, and yellow fever. Serologic results excluded these illnesses.

RNA was extracted by using the TRIZOL LS (Invitogen, Carlsbad, CA, USA) reagent method according to the manufacturer's instructions. Envelope (E)2 and E1 genes of the MAYV genome were amplified by using a standard 1-step reverse transcription–PCR protocol, as pre-

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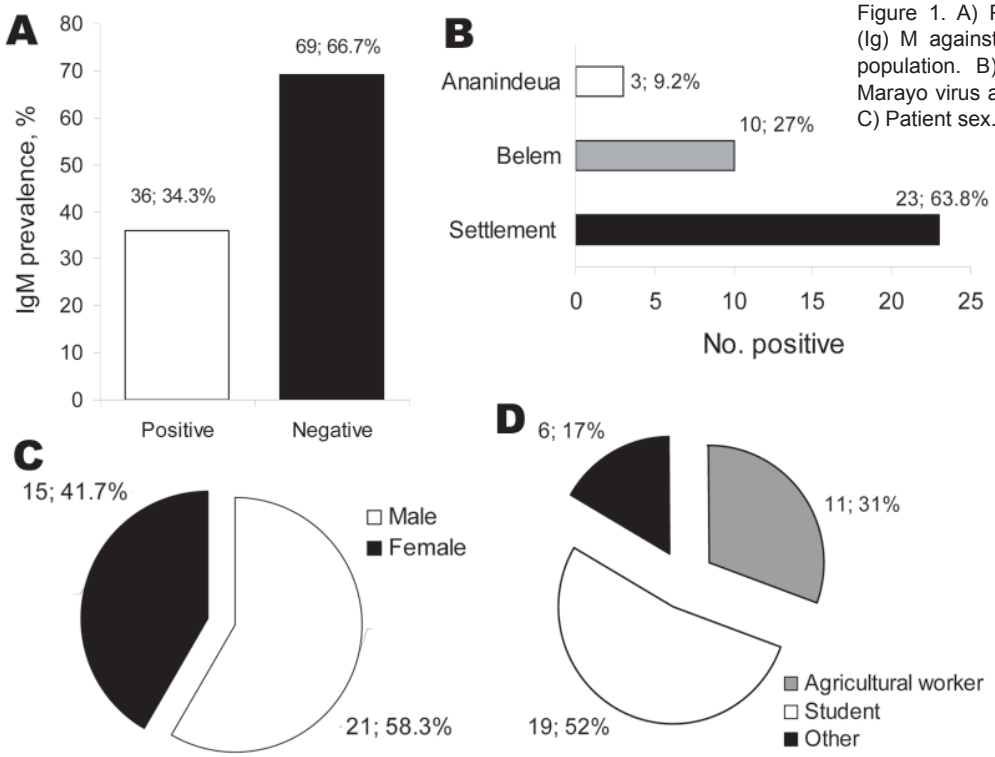

Figure 1. A) Prevalence of immunoglobulin (Ig) M against Mayaro virus in the studied population. B) Prevalence of IgM against Marayo virus according to area of residence. C) Patient sex. D) Patient work activities.

viously described (*1*). The cDNA products were directly sequenced (*6*).

We conducted phylogenetic analysis by using the maximum parsimony (heuristic algorithm), neighbor-joining (Kimura 3-parameter and F84 corrections), and maximum-likelihood methods (*7*) implemented in the PAUP software (*8*) for the nucleotide sequences obtained for the isolates and representative members of other Mayaro-related viruses belonging to the genus *Alphavirus* available at GenBank (www.ncbi.nlm.nih.gov). Bootstrap resample method (1,000 replicates) and outgoup definition were used to provide confidence for the phylogenetic groups (*9*).

The 3 MAYV isolates were successfully sequenced, and the nucleotide sequences covering the 3′ E1 region, the entire E2 gene, and 3′ noncoding region (≈2,000 nt) were phylogenetically compared with other MAYV and Mayaro-related viruses isolated during different periods (1954–2008) and from different hosts (human and arthropods) in Brazil, Peru, French Guiana, Trinidad and Tobago, Suriname, and Bolivia (Figure 2).

The phylogram depicted a clear segregation of MAYV strains into 2 major groups: genotypes D and L (*1*). The strains isolated in Santa Barbara municipality were grouped together in genotype D within clade I. Genetically, these strains were closely related to a 1991 isolate from Tocantins state in northern Brazil. The strains isolated in Santa Barbara were similar to those isolated in Belém during the same period. Interestingly, the Santa Barbara and Belém strains differed from the Brazilian and prototype strains isolated in 1955 (Figure 2).

Conclusions

MAYV has been isolated only in northern South America. Probably because of the short viremic period, it is sporadically isolated only during enzootic periods. However, during epidemics or epizootics, the number of isolates increase sharply (*10*,*11*). The few isolates obtained are intriguing and contrast with the high prevalence of specific antibodies in Pan-Amazonia; previous studies have shown widespread immunity in the Amazon, ranging from 5% to 60%. Positivity increases with age and is higher in rural and neighboring communities, as observed for the Amerindians (*2*,*12*,*13*).

In a previous outbreak in Belterra, several patients were too ill to continue their daily activities while febrile, and some even became prostrate. Moreover, these patients frequently reported severe arthralgia that led to temporary incapacitation (*13*,*14*).

Our data confirmed the occurrence of a Mayaro fever outbreak in the Pau D'Arco settlement. Clinically, the disease was similar to other outbreaks and characterized mainly by fever, arthralgia, myalgia, headache, rash, and dizziness (*2*,*13*–*15*). This outbreak was reported 17 years after the last episode of the disease described in the municipality of Benevides, which is closer (≈10 km) to Santa Barbara (P.F.C. Vasconcelos, unpub. data). The clinical and labora-

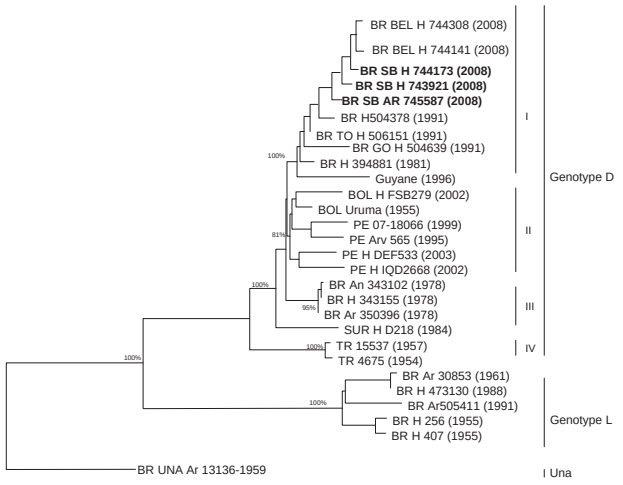

Figure 2. Comparison of genetic relationships among the Mayaro virus strains sequenced in this study with those isolated in different areas of South America, periods of time, and hosts. Numbers above and within parentheses correspond to bootstrap support values for the specific clades. The Una virus was used as an outgroup to root the tree. BR, Brazil (BEL, Belém; SB, Santa Barbara [bold]; TO, Tocantins state); BOL, Bolivia; PE, Peru; SUR, Suriname; H, human; Ar, arthropod. Numbers in parentheses correspond to the year of isolation of each strain. Items in **boldface** indicate strains isolated in this study.

tory data from this MAYV outbreak caused by genotype D confirmed in Santa Barbara provide a better understanding of the MAYV molecular epidemiology in the Brazilian Amazon region.

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Hemorrhagic Fever with Renal Syndrome in 4 US Soldiers, South Korea, 2005

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Four US soldiers acquired hemorrhagic fever with renal syndrome while training near the Demilitarized Zone, South Korea, in 2005. Hantaan virus sequences were amplified by reverse transcription–PCR from patient serum samples and from lung tissues of striped field mice (*Apodemus agrarius*) captured at training sites. Epidemiologic investigations specified the ecology of possible sites of patient infection.

Hantaan virus (HTNV), the etiologic agent for hemorrhagic fever with renal syndrome (HFRS), accounts for ≈70% of all HFRS cases in South Korea and is the most severe of the 4 rodent-borne hantaviruses (Seoul virus, Soochong virus, and Muju virus) found there (*1*–*3*). Recently, a shrew-borne hantavirus, Imjin virus, was isolated from Ussuri white toothed shrews (*Crocidura lasiura*) captured near the Imjin River in South Korea (*4*). The reservoir host of HTNV, the striped field mouse (*Apodemus agrarius)*, is the most abundant field rodent found in South Korea. We conducted an epidemiologic investigation for rodents at 6 training sites near the Demilitarized Zone after 4 US soldiers acquired HFRS in 2005, because no evidence of rodent activity was found where the soldiers worked or resided at their base camp (Camps Hovey and Casey).

The Study

On October 27, 2005, a US soldier (patient 1) assigned to Camp Hovey, Dongducheon, exhibited signs and symptoms of HFRS (Table 1). The patient was transferred to the Brian Allgood Army Community Hospital (BAACH), Yongsan Army Garrison, Seoul, South Korea, and on October 28, 2005, was confirmed to be seropositive for hantavirus infection by ELISA. A medical advisor initially suspected that the patient may have acquired the infection while sweeping out a dusty storage area at Camp Hovey, where he resided, ≈3 days before the onset of symptoms. A survey of the suspected storage room did not uncover any signs of rodent activity. These data along with the known incubation period of hantaviruses (4–>50 days) prompted a further search for the actual site of transmission.

A blood sample from patient 1, tested by both the indirect immunofluorescent antibody (IFA) technique and reverse transcription–PCR (RT-PCR), confirmed that the patient was infected with HTNV. An epidemiologic survey was conducted, and results showed that the patient had trained at 4 US- and South Korea–operated training sites from 26 to 35 days before the onset of symptoms. The patient had first trained at local training area (LTA) 320, then at LTA 36/37, and finally at firing point (FP)-60 (Figure 1). The training consisted of setting up firing positions, establishing a cantonment site, and performing other training activities for 5 days before moving on to FP-60, where troops conducted firing exercises from September 25–29, 2005, before returning to Camp Hovey.

On November 8–9, 2005, two soldiers (patients 2 and 3) from Camp Casey, Dongducheon, had signs and symptoms of HFRS and so were sent to the BAACH where they received a diagnosis of HFRS (Table 1). Patient 4 from the same unit sought treatment at the Camp Casey Troop Medical Clinic on November 13 with low-grade fever, decreased appetite, abdominal pain, chills, low back pain, nausea, and vomiting, and was provided fluids and assigned to quarters (home bed rest). On November 14, laboratory results indicated a nonspecific proteinuria characteristic of HFRS infections, and the patient was transported to the BAACH, where HFRS was diagnosed. Blood samples from all 3 patients were positive for HTNV by IFA and RT-PCR. All 3 patients had trained at Twin Bridges Training Area (TBTA) with potential incubation periods that ranged from 16 to 35 days, and 2 (patients 2 and 4) had trained together at Rodriguez and Watkins Ranges 3 days before conducting a tactical move to TBTA (Table 1; Figure 1). Patients 2 and 4 conducted training at TBTA-North (N) and TBTA-South (S), and patient 3 only conducted training at TBTA-N.

Small mammal trapping was conducted at US and South Korea–operated training sites where the HFRS patients had previously trained within 60 days. Preseasonal (September) *A. agrarius* mice trapping rates were relatively low at both FP-60 (11.4%) and Rodriguez Range (7.6%), and although postseasonal trapping rates were high at FP-60

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Table 1. History of patients who acquired hantavirus infections while training near the Demilitarized Zone, South Korea, during 2005*†

Patient no.	Onset‡	TMC report	Date of diagnosis§	Date confirmed¶	Ribavirin therapy	Date discharged	Training dates (all locations)	Incubation period, d	Training dates (infection source)	Estimated incubation period, d
1	Oct 25	Oct 27	Oct 28	Nov 1	Oct 30	Nov 5	Sep 20–29	26–35	Sep 25–29 (FP-60)	26–30
2	Nov 3	Nov 8	Nov 9	Nov 12	Nov 9	Dec 8	Oct 8–21	13–26	Oct 8–18 (TBTA-S)	16–26
3	Nov 5	Nov 9	Nov 12	Nov 16	Nov 13	Nov 20	Oct 8–15	21–28	Oct 8–15 (TBNA-N)	21–28
4	Nov 12	1st, Nov 13; 2nd, Nov 14	Nov 15	Nov 17	No	Nov 20	Oct 8–21	22–35	Oct 8–18 (TBTA-S)	25–35

*TMC, Troop Medical Clinic; HFRS, hemorrhagic fever renal syndrome; FP, firing point; TBTA, Twin Bridges Training Area; S, south; N, north.
†HFRS type was Hantaan virus for all infections. Patients 1 and 3 were hospitalized for 8 days, patient 4 for 5 days, and patient 2 for 29 days. Patient 2 was sent to Samsung Hospital for dialysis during part of his hospitalization at Brian Allgood Army Community Hospital (BAACH). US Army Medical Department–Korea does not have dialysis capability.
‡Onset of symptoms.
§Diagnosis by ELISA at BAACH.
¶Confirmation of hantavirus type by reverse transcription–PCR, Korea University.

(42.3%), they remained relatively low at Rodriguez Range (15.7%) (Table 2). During the fall, hantavirus seropositive rates were high at FP-60 (20.0%) and Rodriguez Range (31.3%). During the winter, seropositive rates increased at FP-60 (25.8%), but decreased at Rodriguez Range (12.1%). During the winter, seropositive rates at TBTA-N (26.3%) and TBTA-S (37.8%) were high, but were relatively low at other training sites (LTA320/36/37) surveyed.

Blood samples from each of the 4 patients and lung tissues of seropositive rodents were assayed by RT-PCR. RNA extracted by using RNA-Bee isolation kit (TEL-TEST Inc., Friendswood, TX, USA) was reverse transcribed by using the superscript II RNase H-reverse transcriptase kit (GIBCO-BRL, Gaithersburg, MD, USA). Primers (outer primer set, 5′-TGGGCTGCAAGTGC-3′, 5′-ACATGC TGTACAGCCTGTGCC-3′; inner primer set, 5′-TGGGCTGCAAGTGCATCAGAG-3′, 5′-AT GGATTACAACCCCAGCTCG-3′) amplified a 373-nt region of the hantavirus G2-encoding medium (M) segment (*1*,*5*,*6*). Amplified products were fractionated according to size by electrophoresis on 1.5% agarose gels containing ethidium bromide (0.5 mg/mL). DNA sequencing was performed in both directions, by using the dye primer cycle sequencing ready reaction kit (Applied Biosystems, Foster City, CA, USA) on an automated sequencer (Model 3730XL; Applied Biosystems).

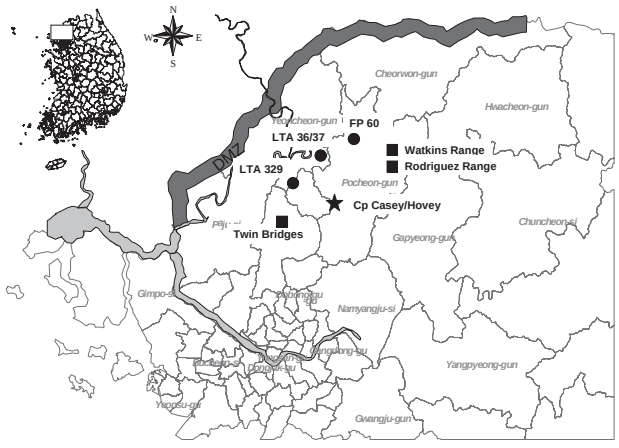

Figure 1. Location of training sites where hemorrhagic fever with renal syndrome (HFRS) patients 1–4 conducted training exercises 50 days before the onset of illness. Rodent surveillance was not conducted at Watkins Range due to limited exposure. DMZ, Demilitarized Zone; LTA, local training area; solid circles, military training sites of patient 1; solid squares, military training sites of patients 2, 3, 4; star, base camp.

Phylogenetic analysis, both neighbor-joining and maximum-parsimony methods, based on the 320-nt region of the G2 glycoprotein–encoding M segment of the 4 HFRS patients, and HTNV sequences amplified from the *A. agrarius* mice captured at FP-10, FP-60, TBTA-N, and TBTA-S demonstrated that the HTNV sequence amplified from patient 1 was identical to sequences from *A. agrarius* HTNV strain (04–1325) at FP-60. The analyses also demonstrated that the HTNV sequences from patients 2 and 4 were identical to *A. agrarius* HTNV sequence (05–1437) at TBTA-S, and the HTNV sequence from patient 3 was identical to *A. agrarius* HTNV sequences (07–196 and 05–1465) at TBTA-N. These data demonstrate the most likely site of infection for the 4 HFRS patients (Figure 2).

Conclusions

The relationships between rodent density, the proportion of hantavirus-seropositive rodents, and incidence of human infection are complex and poorly understood (*7*,*8*). Previous literature indicates that a prevalence of hantavirus seropositivity >20% among *A. agrarius* mice greatly increased the risk for transmission (*9*–*11*). Although monitoring rodent populations may provide some warning, the most effective means of controlling hantavirus infections is

Table 2. Results of rodent-borne disease surveillance at FP 60 and LTAs 36, 37, and 320, Rodriguez Range and Twin Bridges Training Area (South and North Bowls), Gyeonggi Province, South Korea, 2005*

Location	Spring		Summer		Fall		Winter	
	Trapping rate† (%)	Seropositive rate (%)	Trapping rate (%)	Seropositive rate (%)	Trapping rate (%)	Seropositive rate (%)	Trapping rate (%)	Seropositive rate (%)
FP 60	21/220 (9.5)	2/21 (9.5)	89/220 (40.5)	12/89 (13.5)	25/220 (11.4)	5/25 (20.0)	93/220 (42.3)	24/93 (25.8)
LTA 36/37	ND	ND	ND	ND	ND	ND	23/90 (25.6)	0/23 (0)
LTA 320	ND	ND	ND	ND	ND	ND	26/90 (28.9)	2/26 (7.7)
Rodriguez	38/180 (21.1)	3/38 (7.9)	29/210 (13.8)	7/29 (24.1)	16/210 (7.6)	5/16 (31.3)	33/210 (15.7)	4/33 (12.1)
TBTA-N	ND	ND	ND	ND	ND	ND	19/180 (10.6)	5/19 (26.3)
TBTA-S	ND	ND	ND	ND	ND	ND	45/180 (25.0)	17/45 (37.8)

*FP, firing point; LTAs, local training area; ND, not determined; TBTA, Twin Bridges Training Area; N, north; S, south.
†Trapping rate, total number of rodents trapped/number of traps.

limiting human contact with rodents and the inhalation of dust with virus-laden rodent excreta (*12*).

The large patches of tall dense grasses narrowly separated by barren ground where artillery firing is conducted at FP-60 provide harborage for *A. agrarius* mice and, during the winter trapping period, yielded ≈20% capture rates (*10*). Eliminating these large grassy islands, and thus the rodents that inhabit these areas, and cutting the tall grasses and scrub vegetation to <10 cm along the training site perimeter would decrease hantavirus infection risks by re-

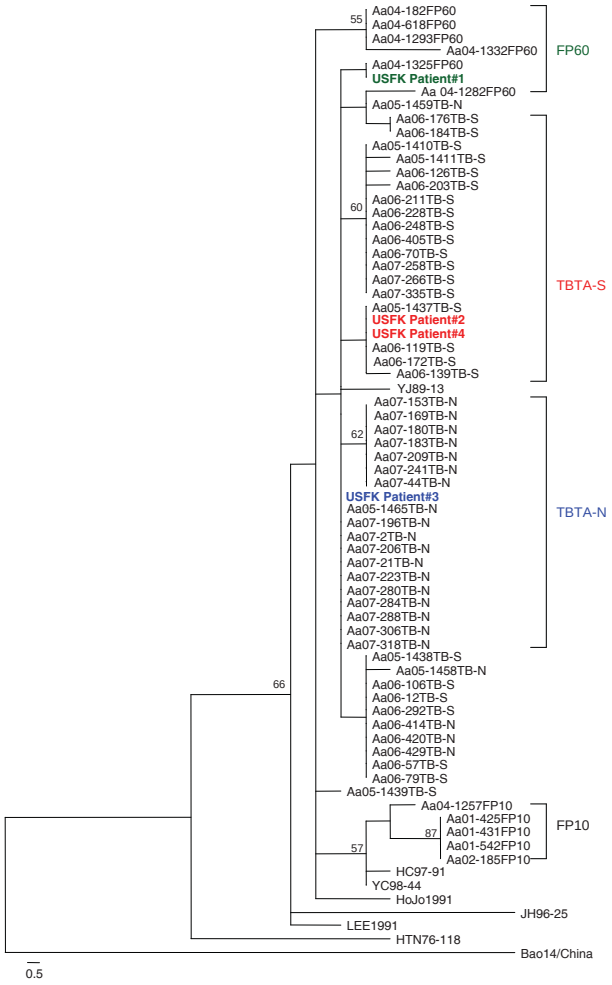

Figure 2. Phylogenetic tree by maximum parsimony method, rooted at the midpoint, based on the 320-bp region of G2 glycoprotein–encoding medium segment of 4 hemorrhagic fever with renal syndrome patients who were US soldiers in South Korea (patients 1–4), 2005 (GenBank accession nos. FJ561275–FJ561278) and field mice (*Apodemus* spp.)–borne Hantaan viruses (HTNV). HTNV sequence amplified from patient 1 was identical with a HTNV sequence (Aa04–1325) from *A. agrarius* mice captured at firing point (FP) 60. HTNV sequences from patients 2 and 4 were the same as 3 HTNV sequences (Aa05–1437, Aa06–119, Aa06–171) from *A. agrarius* mice captured at Twin Bridge Training Area–South (TBTA-S), and the HTNV sequence from patient 3 was identical to 11 HTNV sequences (Aa05–1465, Aa07–2, Aa07–21, Aa07–196, Aa07–206, Aa07–223, Aa07–280, Aa07–284, Aa07–288, Aa07–306 and Aa07–318) from *A. agrarius* mice at Twin Bridge Training Area-North (TBTA-N). Branch lengths are proportional to the number of nucleotide substitutions, while vertical distances are for clarity only. The numbers at each node are bootstrap probabilities (expressed as percentages), as determined for 100 iterations by using PAUP version 4.0b (http://paup.csit.fsu.poly). The colors indicate patients and corresponding training sites.

ducing the rodent populations. Efforts to mitigate disease risks through modernization of training sites, cutting of vegetation that increases predation of small mammals, and habitat reduction within 50 m of military operations, where possible, are being instituted at selected US-operated training sites as a result of consolidation and modernization of large, multipurpose range complexes.

Previously, phylogenetic analysis of a 324-nt region of the G2 glycoprotein-encoding M genomic segment has been shown to be representative of the entire M segment (*6*). This region may be useful for classifying newly identified hantaviruses (when cross-neutralization data are unavailable) or for further analysis of molecular phylogeny of hantaviruses spatially. The genome of HTNV sequences obtained from patient 1 was identical to a viral sequence from an *A. agrarius* field mouse captured at FP-60 and those from patients 2 and 4 were identical to 3 viral sequences from *A. agrarius* at TBTA-South, and patient 3 was identical to 11 viral sequences from *A. agrarius* field mice at TBTA-North. These data showed the epidemiologic link between US soldier patients and rodent hosts at the training sites near the Demilitarized Zone in South Korea.

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Fatal Case of Enterovirus 71 Infection, France, 2007

Sophie Vallet, Marie-Christine Legrand-Quillien, Thomas Dailland, Gaëtan Podeur, Stéphanie Gouriou, Isabelle Schuffenecker, Christopher Payan, and Pascale Marcorelles

A fatal case of enterovirus 71 infection with pulmonary edema and rhombencephalitis occurred in Brest, France, in April 2007. The virus was identified as subgenogroup C2. This highly neurotropic enterovirus merits specific surveillance outside the Asia-Pacific region.

Enterovirus 71 (EV71), like other enteroviruses (family *Picornaviridae*), induces mostly asymptomatic or clinically benign infections. The virus is a leading cause of foot and mouth disease and, above all, is an emerging agent of acute central nervous system disease (aseptic meningitis, flaccid paralysis, encephalitis). Since its identification in 1969, EV71 has been the subject of several studies, particularly over the past decade in the Asia-Pacific region where several outbreaks have been reported (*1*–*5*). Epidemics have also been described in the United States, Brazil, and Europe (Sweden in 1974, Bulgaria in 1975, and Hungary in 1978) (*6*). EV71 can be divided into 3 independent genogroups by molecular typing: A, B, and C (*1*). Genogroups B and C can be further subdivided into subgenogroups B1–B5 and C1–C5 (*6*). Subgenogroups can replace each other within a short period of time, but several genotypes can also cocirculate as seen in Malaysia (*2*).

Death caused by this virus occurs rarely; young children are especially at risk. This report describes a fatal case of acute pulmonary edema with rhombencephalitis that occurred within the course of an EV71 infection in France.

The Case-Patient

In April 2007, a 17-month-old boy was referred to the pediatric emergency ward of the Brest University Hospital. He had hyperthermia, which had begun 48 hours earlier. Upon arrival, he appeared to be in good general condition, despite mild respiratory discomfort and episodes of vomiting. Nasopharyngitis was diagnosed. He was discharged with treatment consisting of symptomatic medication and oral rehydration.

He was readmitted to the pediatric emergency unit 12 hours later, in severe respiratory distress. Disorders of consciousness and drowsiness were observed. He was immediately given supportive intravenous corticotherapy in association with aerosol and oxygen therapy. He was subsequently transferred to the pediatric intensive care unit. Results of his chest radiograph were normal. Laboratory test results were as follows: leukocytosis 23,300/mm^3 (67.5% polynuclear neutrophils), platelets 453,000/mm^3, hemoglobin 116 g/L, and hematocrit 34.9%. The C-reactive protein value was elevated (11 mg/L) and liver function was conserved. Severe dyspnea, hyperglycemia (2.02 g/L), and a decreased blood pressure (38 mm Hg) rapidly developed. After the onset of this acute respiratory distress syndrome, a second chest radiograph showed marked lung infiltration. The patient was intubated because of increased oxygen dependence. Cardiorespiratory arrest occurred during the induction of anesthesia. Despite cardiopulmonary resuscitation, he died <12 hours after his second admission to the pediatric emergency ward.

An autopsy was performed with the prior consent of the parents. Pulmonary edema and multiple foci of polymorph inflammatory infiltrate were present in lung samples. Encephalitic necrotic lesions were multifocal but predominant in the inferior brainstem and superior cervical medulla. Respiratory centers were affected, as were vegetative nucleates of the medulla oblongata (Figure 1). No inflammatory or necrotic areas were found in cardiac muscle.

An enterovirus was isolated in the MRC-5 cell culture from a bronchial aspirate taken just before death. An enterovirus was also isolated in an autopsy nasal swab. Other autopsy samples (lung, spleen, and urine) were positive for enterovirus by reverse transcription–PCR (RT-PCR) (Enterovirus consensus kit, Argene, Verniolle, France), but no virus was isolated from these samples. Brain tissue could not be used for virologic studies because of formalin fixation. The enterovirus strain isolated in cell culture was sent to the French National Reference Centre for Enteroviruses, where it was identified as EV71 by partial viral protein (VP) 1 sequencing (*7*). A second analysis was performed that targeted the 891 nucleotides of the VP1 gene, as described by Bible et al. (*8*). This sequence was compared by phylogenetic analysis with 34 GenBank-selected VP1 enterovirus 71 strains (Table). A phylogenetic tree was constructed by neighbor-joining, using the Kimura 2-parameter distance method to define relationships between the current isolate and other EV71 subgenogroups. The VP1 sequence of the French patient who died clustered with VP1 sequences belonging to the C2 subgenogroup (Figure 2).

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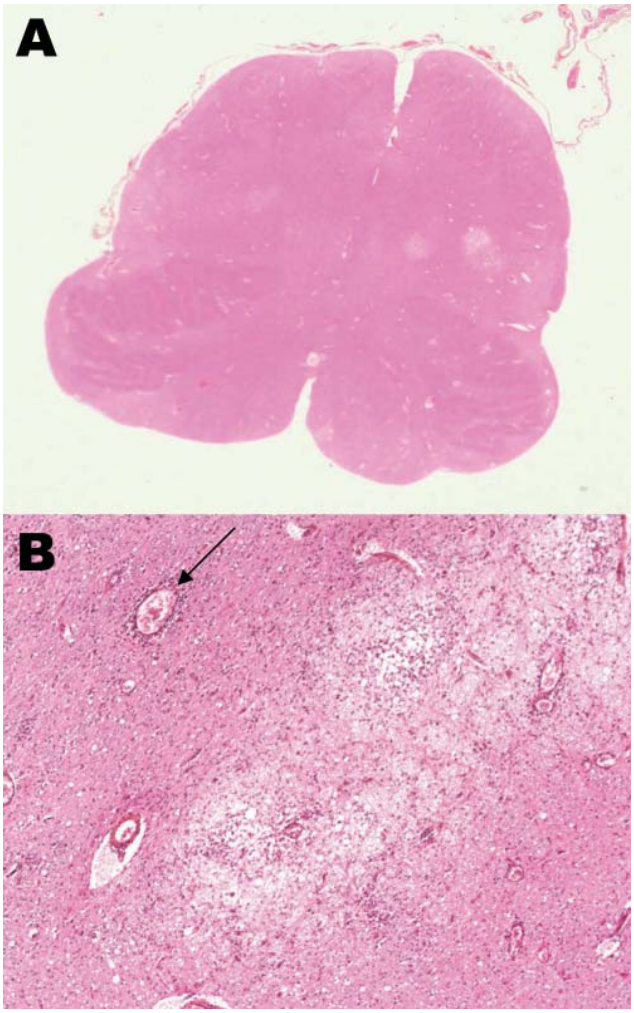

Figure 1. A) Horizontal section of the medulla at the level of the inferior olivari nuclei, showing multiple inflammatory areas (clear areas); original magnification ×4. B) Severe edematous area with inflammatory cells, macrophages, edema, and perivascular cuffing (arrow); original magnification x200, hematoxylin-eosin stain.

The 2 closest-matching isolates originated from 2 young children admitted to the Brest Hospital emergency ward a few months later, in June and July 2008, respectively. The first, 13 months of age, was admitted for acute respiratory syndrome, which rapidly resolved. Enterovirus 71 was isolated from the child's bronchial secretions. The second child, 31 months of age, had acute gingivostomatitis, fever, and cerebellar syndrome evocative of meningoencephalitis. Enterovirus was isolated from buccal lesions, but no virus was detected by RT-PCR in cerebrospinal fluid (CSF), even though pleocytosis was present. He recovered quickly. The VP1 full-length sequences of the 3 strains were deposited in GenBank under the accession nos. FJ824734–FJ824736. The high nucleotide identity among the 3 strains (>98%), and their place and period of circulation suggest a probable identical ancestral strain, which remains undefined. The origin of the EV71 strain responsible for the substantial pulmonary edema described here remains unknown. The 3 strains isolated clustered with 3 other European strains, isolated in 2006 and 2008 in the United Kingdom (*8*,*9*), and

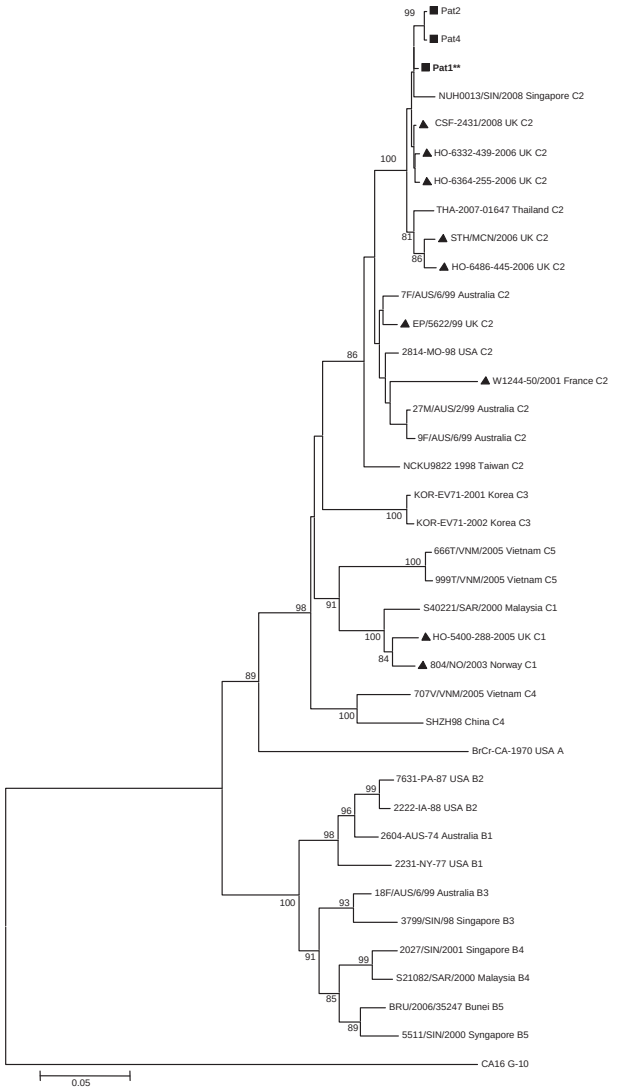

Figure 2. Phylogenetic relationships between 3 French strains and 34 worldwide enterovirus 71 GenBank-selected strains based on alignment of complete viral protein (VP) 1 coding sequences. The prototype coxsackievirus A16 (CoxA16-G10) was used as the outgroup virus. The phylogenetic tree was constructed by the neighbor-joining method by using MEGA4 (www.megasoftware.net). Bootstrap values (>70%) derived from 1,000 samplings are shown at the nodes of the tree. Phylogenetic separation of C2 isolates appear in accordance with time and place of isolation. Isolates from this study are indicated by black squares (the strain isolated from the 17-month-old boy with fatal pulmonary edema is shown in boldface with **), and the other European circulating strains by black triangles. Branch lengths are drawn to scale. Scale bar indicates 5% of nucleotide sequence divergence.

Table. EV71 clinical strains used in phylogenetic analysis of the complete VP1 gene*

GenBank accession no.	Year	Origin	Clinical features	Isolate	Genogroup	Reference
U22521	1970	USA	Encephalitis	BrCr-CA-70	A	(*1*)
AF135883	1974	Australia	Meningitis	2604-AUS-74	B1	(*1*)
AF135870	1977	USA	NA	2231-NY-77	B1	(*1*)
AF009533	1987	USA	Gastroenteritis	7631-PA-87	B2	(*1*)
AF009540	1988	USA	Fever	2222-IA-88	B2	(*1*)
AF376117	1998	Singapore	HFMD	3799/SIN/98	B3	(*2*)
AF376095	1999	Australia	HFMD	18F/AUS/6/99	B3	(*2*)
AF376084	2000	Sarawak	HFMD	S21082/SAR/2000	B4	(*2*)
AF376111	2000	Singapore	NA	2027/SIN/2001	B4	(*2*)
AF376121	2000	Singapore	HFMD	5511/SIN/2000	B5	(*2*)
FM201341	2006	Brunei	NA	BRU/2006/35247	B5	(*5*)
AF376087	2000	Sarawak	HFMD	S40221/SAR/2000	C1	(*2*)
DQ452074	2003	Norway	NA	804/NO/2003	C1	(*10*)
AM939598	2005	UK	Unspecified neurologic disease	HO-5400-288-05	C1	(*8*)
AF135950	1998	Missouri	Meningitis	2814-MO-98	C2	(*1*)
AF136379	1998	Taiwan	Death	NCKU9822	C2	(*3*)
AM939583	1999	UK	Aseptic meningitis	EP/5622/99	C2	(*8*)
AF376108	1999	Australia	Meningitis	7F/AUS/6/99	C2	(*2*)
AF376102	1999	Australia	HFMD	27M/AUS/2/99	C2	(*2*)
AF376110	1999	Australia	Ataxia	9F/AUS/6/99	C2	(*2*)
AY208099	2001	France	Guillain-Barré syndrome	W1244-50/2001	C2	(*11*)
AM939604	2006	UK	Meningitis	HO-6332-439-06	C2	(*8*)
AM939607	2006	UK	Irritable, rash	HO-6364-255-06	C2	(*8*)
AM939597	2006	UK	Panencephalitis, fatal	STH/MCN/06	C2	(*8*)
AM939599	2006	UK	Difficulty walking	HO-6486-445-06	C2	(*8*)
FJ461786	2008	Singapore	NA	NUH0013/SIN/2008	C2	UD
FJ151492	2007	Thailand	NA	THA-07-01647	C2	UD
FJ525952	2008	Edinburgh	NA	CSF-2431/2008	C2	(*9*)
AY125966	2001	Korea	NA	KOR-EV71-01	C3	UD
AY125967	2002	Korea	NA	KOR-EV71-02	C3	UD
AF302996	1998	China	NA	SHZH98	C4	UD
AM490154	2005	Vietnam	NA	707V/VNM/2005	C4	(*4*)
AM490163	2005	Vietnam	NA	999T/VNM/2005	C5	(*4*)
AM490153	2005	Vietnam	NA	666T/VNM/2005	C5	(*4*)

*EV, enterovirus; VP, viral protein; HFMD, hand, foot, and mouth disease; NA, not available; UD, unpublished data.

with 2 Asian strains, isolated in 2007 in Thailand and in 2008 in Singapore and Thailand (GenBank, unpub. data).

Conclusions

Acute pulmonary edema in EV71 infections was rarely reported before the 1998 outbreak in Taiwan (*12*). Since then, this disease, which is often fatal, has been more frequently described, with known prognostic factors, including clinical and biologic features such as central nervous system involvement, leukocytosis, decreased blood pressure, and hyperglycemia (*13*). The fatal infection reported here, which ran a biphasic course, featured all of these signs, with death occurring within a few hours of the onset of respiratory distress. This devastating syndrome is believed to result from the extensive damage of bulbar vasomotor and respiratory centers (Figure 1). In the study by Kao et al. all 21 patients who had acute pulmonary edema associated with these signs died within 4 hours of the development of acute respiratory distress syndrome (*13*).

No reports of fatal cases of EV71 infection in Europe have been made since cases were reported in Hungary in 1978 (*9*–*11*,*14*) with the exception of a fatal case of panencephalitis associated with subgenogroup C2 in the United Kingdom (*8*). No single neurovirulent genotype appears to be associated with severe and fatal cases; at least 3 separate genotypes have been isolated from patients with fatal cases in Malaysia (Sarawak), Japan, and Taiwan (*6*). A similar subgenogroup such as C1 may be associated with complicated disease in Sarawak and asymptomatic infection in Norway (*2*,*10*). A specific marker for virulence has yet to be defined.

Further studies are required to estimate the prevalence of EV71 infection, and only extensive clinical, virologic, and anatomopathologic investigation may determine the actual prevalence of EV71 in severe and sometimes fatal neurologic diseases. EV71, like poliovirus, is not always recovered from CSF during central nervous system infection (*15*). This fact underscores the importance of virologic

investigations on peripheral samples (throat swabs, urine, stool, and vesicles).

Since 2006, centers participating in the French Enterovirus Surveillance Network have declared a significantly growing number of EV71 infections (D. Antona, pers. comm.). The international spread of EV71 outside the Asia-Pacific region needs to be vigilantly monitored, because both the possibility of an outbreak and the unpredictability of virus circulation patterns represent a public health concern.

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Dr Vallet is a microbiologist involved in the study of viral genetic diversity and phylogenic analyses. She works in the virological unit of Brest University Hospital, which is a member of the French Enterovirus Surveillance Network.

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Evidence-based Tool for Triggering School Closures during Influenza Outbreaks, Japan

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Guidelines available to school administrators to support school closure decisions during influenza outbreaks are usually not evidence based. Using empirical data on absentee rates of elementary school students in Japan, we developed a simple and practical algorithm for determining the optimal timing of school closures for control of influenza outbreaks.

Influenza pandemic preparedness and seasonal influenza control programs have focused on vaccine development and antiviral drugs, which are only partially effective and not always available to all persons at risk (*1–3*). Nonpharmaceutical interventions, such as social distancing, represent additional key tools for mitigating the impact of outbreaks. Because children are a major factor in the transmission of influenza within communities and among households, school closure may be a valuable social distancing method (*4,5*).

Japan has a unique system of monitoring school absenteeism and of instituting school closures during influenza outbreaks. Individual classes, specific grade levels, or the entire school may be closed; final decision-making authority is given to school principals. However, as in the United States and other countries, there are no regulations to support these decisions (*6*). Our study suggests a simple system to help determine when schools should be closed; daily influenza-related absentee thresholds are measured to predict outbreaks.

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The Study

We used data on absenteeism caused by influenza from the 54 elementary schools in Joetsu City, Niigata Prefecture, Japan during the 4 influenza seasons during 2005–2008. Data was obtained between the second week of January to the third week of March for each influenza season. Average school size was 221 students. Current public health policy prevents influenza-infected children from attending school until 2 days after fever has disappeared. An illness requires 2 physician visits: 1 for the initial diagnosis and 1 to obtain written permission from the treating physician to return to school. Diagnoses are usually made by using a rapid antigen test and patients are treated with the antiviral drugs, oseltamivir or zanamivir.

Based on elementary school daily influenza-related absentee surveillance, the most intense influenza seasons were 2005 and 2007 (Figure 1). The number of schools reporting outbreaks during the 4 influenza seasons was 34 (63%, 2005), 13 (24%, 2006), 35 (65%, 2007) and 18 (33%, 2008), respectively. Rates of absenteeism caused by confirmed influenza infection in the 54 elementary schools in Joetsu City were well correlated with national reports of influenza-like illness by 5,000 sentinel physicians, who reported 322, 205, 226, and 142 cumulative cases of infection per sentinel in each season (online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1841-Techapp.pdf).

We evaluated the optimal influenza-related absentee rate for predicting outbreaks of influenza. For this study, we defined an influenza outbreak in a school as a daily influenza-related absentee rate of >10%, on the basis of the 95th percentile of daily absentee rates (10.7%) in 54 elementary schools during 4 influenza seasons (online Technical Appendix).

Next, we considered 9 different daily influenza-related absentee threshold levels for initiating early school closures: 1%, 2%, 3%, … , 9%. In addition, for each threshold level, we considered 3 scenarios: 1) a single-day scenario, in which daily influenza-related absentee rates are observed for the first time above a given threshold for 1 day; 2) a double-day scenario, in which rates reached a given threshold for the first time for 2 consecutive days; the rate for the second day was the same or higher than for the first day; and 3) a triple-day scenario, in which rates reached a given threshold for the first time for 3 consecutive days; rates for the second and third days were the same or higher than the rate for the first day. The double-day and triple-day scenarios did not include weekends. To evaluate the performance of prediction for each threshold, we determined the school's outbreak status in the 7-day period starting on the first day of each scenario (online Technical Appendix) JMP7.0.1 (SAS Institute, Inc., Cary, NC, USA) was used for statistical analysis.

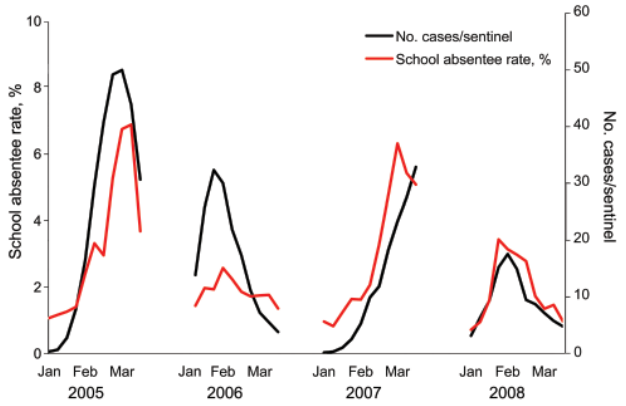

Figure 1. Four-year surveillance of influenza-related absentee rates in 54 elementary schools in Joetsu City and national surveillance of influenza-like illness (ILI) reported by sentinel physicians in Japan. Data were collected from the second week of January (after the winter holiday) to the third week of March (before the spring holiday). The average of the daily absentee rates for 54 elementary schools during 4 influenza seasons (2005–2008) were 3.29%, 1.77%, 2.97%, and 1.92%, respectively.

We calculated the sensitivity and specificity of each scenario at all 9 threshold levels, and presented these data as a plot in Figure 2. The area under the curve for the single-, double-, and triple-day scenarios was 0.80 (95% confidence interval [CI] 0.77–0.83), 0.85 (95% CI 0.82–0.89) and 0.87 (95% CI 0.83–0.91), respectively.

We used the Youden index for calculating optimal thresholds (*7*). The Youden index = (sensitivity) + (specificity) – 1. A perfect test result would have a Youden index of 1. For the single-day scenario, the optimal threshold was 5%, with a sensitivity of 0.77 and specificity of 0.73. For the double-day scenario, the optimal threshold was 4%, with a sensitivity of 0.84 and specificity of 0.77. For the triple-day scenario, the optimal threshold was 3%, with a sensitivity of 0.90 and specificity of 0.72.

Conclusions

We have demonstrated the predictive value of a simple and practical detection method for triggering school closures early after influenza outbreaks. Our analysis suggests that a single-day at a threshold influenza-related absentee rate of 5%, double-days ≥4%, or triple-days ≥3% are optimal levels for alerting school administrators to consider school closure. The double- and triple-day scenarios performed similarly, and gave better results than the single-day. Thus, the double-day scenario might be the preferred early warning trigger.

Our study had the advantage of reliable empirical data on influenza-related absenteeism in schools. Data were based on physician and laboratory diagnosis and a strong absentee surveillance program. However, there are limitations to our approach. We did not have available vaccination or medication histories of patients. Also, our results are based on data from only 1 city's school district; validation in a broader area will be required. Although separate analyses may be required for other geographic regions, we present a simple approach that can be easily reapplied.

Influenza outbreak detection from surveillance data typically relies on relatively complex time series analysis or smoothing (*8*,*9*). The noisiness of school surveillance data makes detection of outbreaks difficult (*10*). However, complex statistical analyses are not practical to use in the context of daily decision-making in schools. Despite the limitations of our study, we have presented a method that provides a basis for empirical data-supported decision-making by school administrators that is intuitive and practical.

School closure could be an effective method of social distancing, although evidence supporting its effectiveness is incomplete. Some studies suggest that though child-to-child transmission might decrease, transmission might increase in other age groups (*11*,*12*). During school closures, children may need to forgo participation in external activities that could increase contact rates. Additionally, working parents staying home to care for their children (*13*) could result in a decrease in household income, causing loss of productivity and economic losses (*14*). Decision-makers will need to consider these factors when considering school closures.

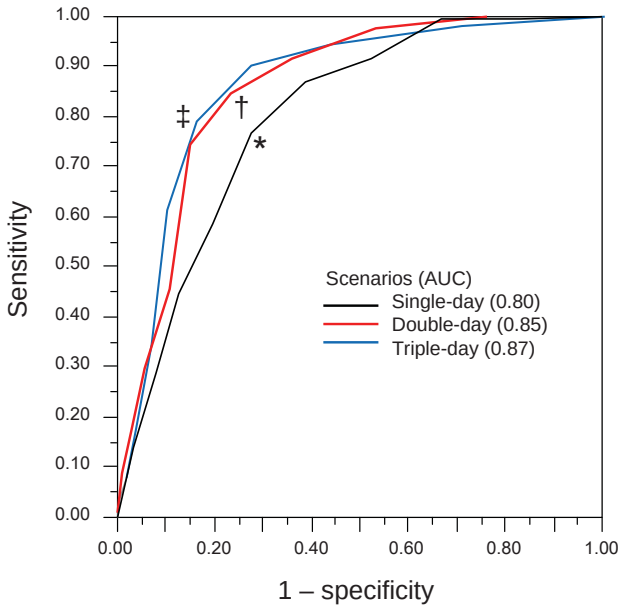

Figure 2. The receiver operating characteristic (ROC) curve for detection of influenza outbreak by 1%–9% thresholds under single-day, double-day, triple-day scenarios. ROC space is defined on the x axis as specificity and on the y axis as sensitivity. The area under the curve (AUC) is an indicator of the quality of a model; larger AUC values corresponded to better performance. Optimal thresholds for the 3 scenarios are *single-day, 5%; †double-day, 4%; and ‡triple-day, 3%.

During the early days of the outbreak of influenza A pandemic (H1N1) 2009 virus, the US Centers for Disease Control and Prevention (Atlanta, GA, USA) released 2 different recommendations for school dismissal after the appearance of the first suspected case: dismiss for 7 days (as of April 26) and then for 14 days (as of May 1). Later, to reflect new knowledge about the extent of community spread and disease severity, the recommendation was revised to advise against school closure unless absentee rates interfered with school function (*15*). The pandemic (H1N1) 2009 influenza outbreak highlights the need for a flexible national policy that can be quickly adapted to reflect current situations. The evidence-based strategy for predicting outbreaks based on influenza-related absentee rates that we present here provides local administrators, who may need to consider school closure, with a simple and practical tool to aid in their decisions.

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Dirofilaria repens Infection and Concomitant Meningoencephalitis

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Dirofilaria repens, a filarial nematode of dogs and other carnivores, can accidentally infect humans. Clinical symptoms are usually restricted to a subcutaneous nodule containing a single infertile parasite. Here, we report a case of *D. repens* infection with a subcutaneous gravid worm and the patient's concomitant meningoencephalitis and aphasia.

Dirofilaria repens is a filarial nematode that affects dogs and other carnivores. Infections have been reported from various regions of the world, mainly from Europe, Africa, and Asia. As with other filaria species, mosquitoes transmit infectious microfilariae, which develop into fertile macrofilariae in their definitive host. Humans may become infected as aberrant hosts, and, apart from rare exceptions, the worms remain infertile (*1*–*5*). Infections in humans usually manifest as a single subcutaneous nodule, which is caused by a macrofilaria that is trapped by the immune system (*1*,*6*). Subcutaneous migration of the worm may result in local swellings with changing localization (creeping eruption). In addition, rare cases of organ manifestation have been reported, affecting the lung, male genitals, female breast, or the eye. The latter is found in particular during the migratory phase of the parasite (*1*,*5*–*8*). Because typically only a single worm is present, removal of the parasite from the skin is usually sufficient to treat human infections. Final diagnosis is established by microscopic examination of the excised worm (*5*,*6*). Making a definite species diagnosis on morphologic grounds is difficult, because a large number of zoonotic *Dirofilaria* species have been described that share morphologic features with *D. repens.* Further species probably await description. Here, we report an unusual *D. repens* infection in a resident of Germany who returned from travel to India and Sri Lanka with a subcutaneous nodule containing a gravid female worm and concomitant meningoencephalitis. Molecular analysis identified a *D. repens* strain that was different from those found in public databases.

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The Case

Two days after returning from 9 months of travel in southern India and Sri Lanka, a 45-year-old German man sought treatment at a hospital because of acute speech problems. During the previous 5 weeks, the patient had experienced a persistent headache and creeping eruptions of 5–7 cm on the left arm, which moved from the upper arm to the back of the hand. Physical examination found a tender nodule on the left hand, with a diameter of ≈2 cm, as well as signs of aphasia and apraxia. Cranial magnetic resonance imaging (MRI) indicated cortical and subcortical signal changes in the left frontal region, with signs of meningeal inflammation but no signs of acute ischemia, bleeding, or venous occlusions. Laboratory investigations showed increased cerebrospinal fluid (CSF) protein levels and increased CSF cell counts of 1,500/μL with a high proportion of eosinophils (40%), as well as increased blood leukocyte counts of 12,000/μL (9% eosinophils). Serologic testing showed high antibody titers against *Dirofilaria* antigen and moderate titers against *Strongyloides* antigen, but no significant antibody titers were found against other helminth antigens tested, including *Toxocara, Cysticerca, Schistosoma, Fasciola,* or *Paragonimus* species. Antihelminthic treatment with albendazole (400 mg 2×/d) and concomitantly with methyl-prednisolone (20 mg 2×/d) was initiated, and the patient recovered rapidly.

Removal of the nodule 10 days after the initiation of drug therapy and subsequent histologic examination showed eosinophilic infiltrates and sections of a gravid female nematode that contained large numbers of microfilariae with obtuse cephalic ends and a filiform tail without nuclei. The adult worm showed several characteristics resembling those of *D. repens* (*2*,*5*,*9*,*10*) (Figure). The cuticula was 20 μm thick, multilayered, transverse-striated, and contained large numbers of external longitudinal ridges. Cross-sections showed a well-developed musculature of the coelomyarian type and a worm diameter of ≈550μm. To further confirm the diagnosis of *D. repens* infection, DNA of the worm was extracted (*11*) and panfilarial PCR was performed that targeted the mitochondrial 12S rRNA gene (*11*). Sequence analysis of the 509-bp PCR product and comparison with sequences deposited in GenBank showed the organism had the highest similarity of ≈97% to *D. repens* and of 90% to *D. immitis* (data not shown; the sequence has been submitted to the GenBank database with the accession no. GQ292761).

Conclusions

We report a human *D. repens* infection with concomitant meningoencephalitis. Complications associated with

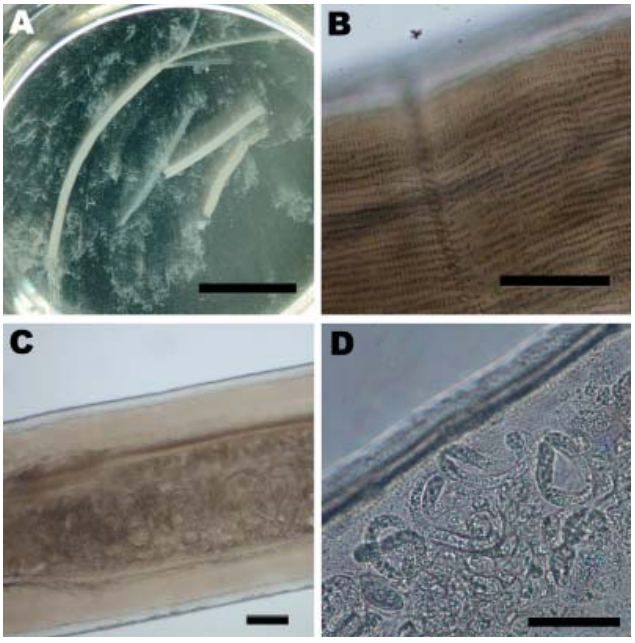

Figure. Images of the adult female *Dirofilaria repens* worm removed from a subcutanous nodule of the patient. A) Macroscopic view of sections of the worm in saline in a petri dish. Two uteri and the intestinal tract can be seen protruding from a disrupted end of the largest section. The saline is turbid due to the massive release of microfilariae, which are not discernible at this magnification. Scale bar = 1 cm. B) Microscopic view of the outer cuticula with multiple longitudinal ridges. Scale bar = 100 μm. C) Microscopic view of the worm showing the well-developed muscle layer and the uterus containing microfilariae. Scale bar = 100 μm. D) Higher magnification of a section of the uterus containing multiple microfilariae. Scale bar = 50 μm.

the central nervous system were most likely because of the worm infection as the CSF contained high numbers of eosinophilic granulocytes, the patient recovered rapidly after initiation of antihelminth and anti-inflammatory treatment, and MRI largely excluded other causes such as acute ischemia, bleeding, or venous occlusions. Other helminth infections, in particular, cysticercosis, were unlikely, according to a panel of negative serologic tests. In contrast to other *D. repens* infections in humans, which are usually restricted to the skin, in this case the patient showed blood eosinophilia and high antibody titers to *Dirofilaria* antigen, which indicate a generalized response to the parasite. Moreover, the worm removed from the skin nodule of the patient had developed to maturity and contained microfilariae. These microfilariae were likely responsible for the generalized immune response as well as for the involvement of the central nervous system. Microfilariae that cross the blood-brain barrier and cause neurologic symptoms in humans or animals have been previously described for other species such as *Meningonema peruzzi* and *D. immitis* (*12*,*13*). In the case presented here, infection was most likely acquired in India or Sri Lanka, 2 regions where *D. repens* is endemic (*7*,*8*,*14*,*15*). Notably, genetic analysis of the highly conserved mitochondrial 12S rRNA gene showed a 3% deviation from *D. repens* sequences deposited in public databases, which suggests that different *D. repens* strains vary considerably. Whether specific variants are more likely to develop to maturity and cause generalized disease in humans deserves further investigation.

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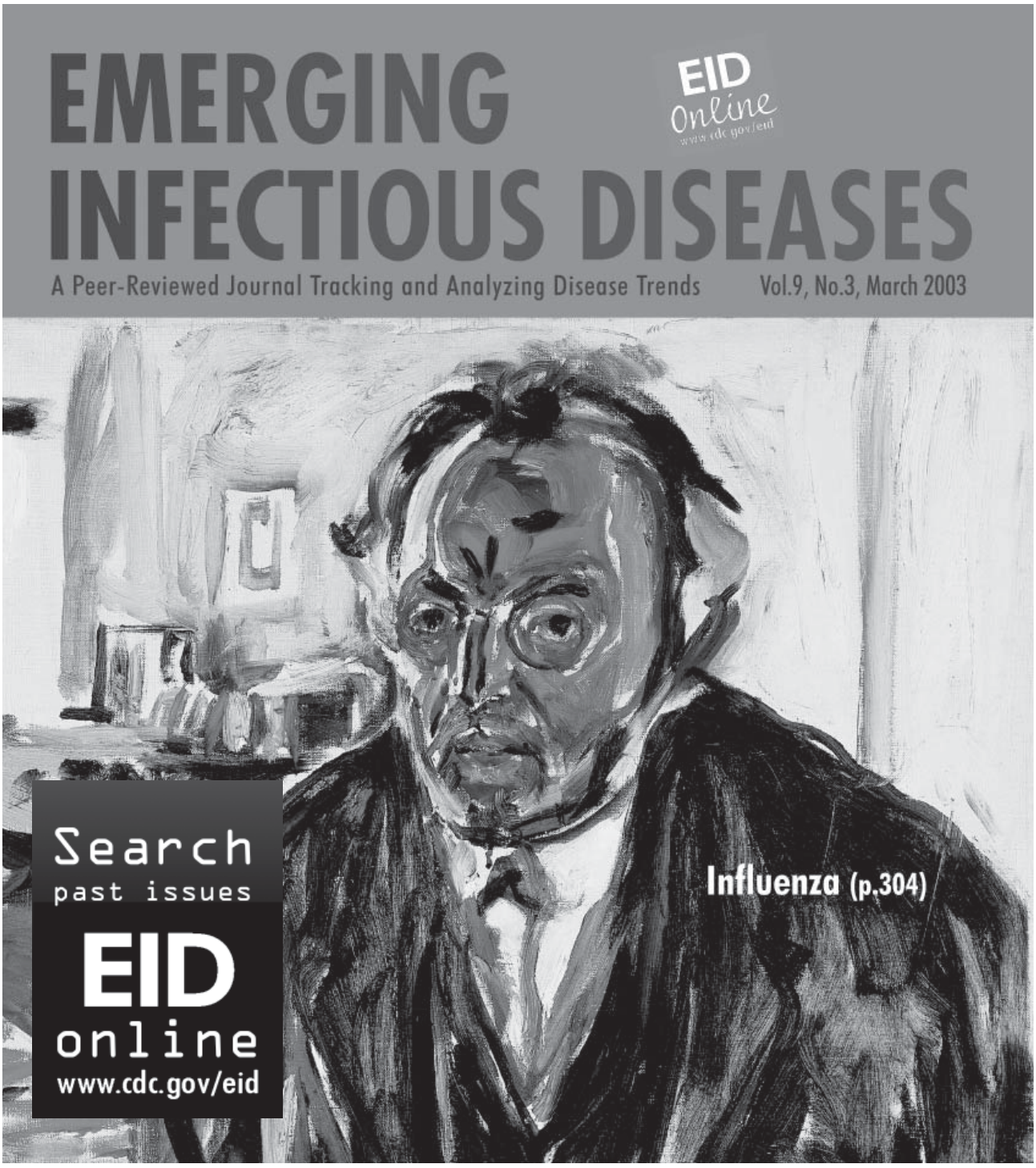

Preexisting Immunity to Pandemic (H1N1) 2009

To the Editor: The influenza A pandemic (H1N1) 2009 virus contains a combination of 8 gene segments (*1*–*3*) antigenically similar to North American influenza A virus (H1N1) but different from seasonal human influenza A viruses (H1N1) (*3*). Despite the initial high number of deaths among patients in Mexico and among patients with specific preexisting conditions, pandemic (H1N1) 2009 virus in general has caused mild symptoms, and the overall death rate remains around 0.45% (www.who.int/csr/don/2009_07_06/en). Low virulence of the virus and preexisting immune status are among the main factors that account for lower death rates in influenza outbreaks. The Centers for Disease Control and Prevention (Atlanta, GA, USA) reported that among persons >60 years old, 33% have preexisting, cross-reactive neutralizing antibodies against the new virus, but seasonal influenza vaccines do not elicit cross-reactive neutralizing antibodies against pandemic (H1N1) 2009 virus in either younger or older populations (*1*). However, current data cannot be used to evaluate the full immune capacities of human populations because cell-mediated immunity (CMI) has not been characterized in humans infected with pandemic (H1N1) 2009 virus.

We performed a survey (*4*) for known human immune epitopes present in the various proteins of seasonal influenza A virus strains and known to be efficient in stimulating lymphocytes. We found that multiple major histocompatibility complex (MHC)–restricted epitopes are conserved in nucleoprotein (NP) and matrix protein (MP), and even a few in the more variable hemagglutinin (HA) protein, in A/California/04/2009, A/Texas/04/2009, and A/New York/18/2009.

For MHC class II antigen-restricted epitopes essential for antibody and Th1 responses, HA of pandemic (H1N1) 2009 virus contains HLA-DRA*0101/DRB1*0101-restricted SVIEKMNTQFTAV (*5*), as well as HLA-DRA*0101/DRB1*0401-restricted EKMNTQFTAVGKE, TGLRNIPSIQSRG, and ELLVLLENERTLDY (*5*), and HLA-DRB5*0101-restricted DYEELREQL SSVSSFERFE (*5*) epitopes. These antigen-restricted epitopes were present in globally-distributed seasonal H1N1 viruses, including classical A/New Caledonia/20/1999 (H1N1) and A/Solomon Islands/3/2006 (H1N1). Overall, high levels of cross-reactive microneutralization (MN) or hemagglutination inhibition (HI) antibodies may not be detected against pandemic (H1N1) 2009 virus. This lack of detection of MN or HI antibodies is probably because most of these epitopes may not elicit MN/HI detectable antibodies, or these epitopes may be present in earlier seasonal influenza strains but not present in the current trivalent, inactivated influenza vaccine. Even though many do not contribute to neutralizing antibodies, these MHC class II antigen-restricted epitopes may initiate the Th1 response, including activation of infected macrophages and antiviral cytokine production, and help host defenses as well.

For MHC class I antigen-restricted epitopes essential for CD8+ T cell activation and CMI, HA of pandemic (H1N1) 2009 virus contains HLA-A*0201-restricted GLFGAIAGFI (*6*), which is present also in the HA of A/New Caledonia/20/1999 (H1N1) and A/Solomon Islands/3/2006 (H1N1) viruses. More MHC class I antigen-restricted epitopes in NP and MP of seasonal epidemic influenza viruses (H1N1) and (H3N2) are conserved in pandemic (H1N1) virus. These seasonal influenza viruses were isolated in North America, Europe, Africa, and Asia–Pacific regions. Conserved epitopes in the HA and NP of pandemic (H1N1) 2009 virus are listed in the Table. In addition, ≈15 completely conserved epitopes are in the M protein of pandemic (H1N1) 2009 virus (data not shown).

Studies have demonstrated that both humoral and cell-mediated immune responses may contribute to protection in influenza-vaccinated persons. As for humoral immunity, results have consistently indicated that serum HI or MN antibody titers correlate inversely with morbidity rates after vaccination, which are the most valuable correlates of protection (*7*). Studies supporting the role of CMI in influenza viral clearance and host survival are well-documented in mouse models, but data are limited for humans. However, emerging evidence has demonstrated that either infection or vaccination can induce T cell-mediated immune responses in humans (*8*,*9*). Moreover, higher levels of CD8+ T cells correlate with reduced viral shedding among experimentally infected humans (*10*). Notably, among vaccinated persons ≥60 years of age, measures of the ex vivo cellular immune response are statistically correlated with protection against influenza illness but serum HI antibody levels are not, suggesting a role for CMI (*9*). Therefore, it is rational to expect that CMI does provide a protective role, and cross-reactive CMI to pandemic (H1N1) 2009 virus through conserved MHC class I-restricted epitopes may exist in persons previously vaccinated for or exposed to seasonal influenza.

We note that ≈80% of MHC class I epitopes in NP of seasonal and flu vaccine viruses (Table) are also completely conserved in the highly pathogenic avian H5N1 virus (A/Hong Kong/156/1997 and A/Hong Kong/97/1998) (www.ncbi.nlm.nih.gov/genomes/FLU). Several points have to be made regarding the relevance of these epitopes to its high associated mortality rate. First, influenza virus (H5N1) is known to be highly virulent, replicating at a much faster

pace than other influenza A viruses and spreading in vital organs shortly after infection and before epitope-mediated protective immunity can be launched, which may account for its high fatality rate. Second, the epitopes are MHC class I antigen-restricted, which means that only a fraction of the human population will possess the correct MHC class I molecules capable of presenting a specific epitope and eliciting appropriate and protective CMI responses. This lack of correct MHC class I molecules could explain why patients of varied genetic backgrounds may have different prognoses upon infection with pandemic (H1N1) 2009 virus or even influenza virus (H5N1).

Table. Conserved MHC class I antigen-restricted epitopes present in HA and NP proteins of pandemic (H1N1) 2009 virus*

MHC antigen	Epitope position	Sequence	Identified in selected virus isolates
HA			
HLA-A*0201	344–353	GLFGAIAGFI	A/New Caledonia/20/1999 (H1N1) A/Solomon Islands/3/2006 (H1N1) A/Macau/229/2008 (H1N1) A/Managua/254.01/2008(H1N1
NP			
HLA-A1 HLA-A*0101	44–52	CTELKLSDY	A/Hong Kong/HKU4/2004 (H3N2) A/Canterbury/200/2004 (H3N2)
HLA-A3	265–273	ILRGSVAHK	A/New Caledonia/20/1999 (H1N1) A/New York/55/2004 (H3N2) A/Managua/254.01/2008(H1N1) A/Taiwan/2645/2006 (H1N1)
HLA-B27	380–393	ELRSRYWAIRTRSG	A/New Caledonia/20/1999 (H1N1) A/Taiwan/2645/2006 (H1N1) A/Managua/254.01/2008(H1N1) A/Florida/UR06-0383/2007(H1N1)
HLA-B27	174–184	RRSGAAGAAVK	A/New Caledonia/20/1999 (H1N1) A/New York/55/2004 (H3N2) A/California/UR07-0067/2008 (H3N2) A/Taiwan/2645/2006 (H1N1)
HLA-B*2705	357–370	KLSTRGVQIASNEN	A/New Caledonia/20/1999 (H1N1) A/New York/55/2004 (H3N2) A/Hong Kong/HKU77/2005 (H3N2) A/Managua/3153.01/2008 (H1N1)
HLA-B*2705	383–391	SRYWAIRTR	A/New Caledonia/20/1999 A/Taiwan/2645/2006 (H1N1) A/Managua/4537.03/2008 (H1N1) A/Florida/UR07-0026/2008 (H1N1)
HLA-B*2702	381–388	LRSRYWAI	A/New Caledonia/20/1999 A/Florida/UR06-0383/2007(H1N1)
HLA-B*4002	251–259	AEIEDLIFL	A/Canterbury/200/2004 (H3N2) A/Hong Kong/HKU71/2005 (H3N2)
HLA-B8	225–233	ILKGKFQTA	A/New Caledonia/20/1999 A/California/UR07-0067/2008 (H3N2) A/Taiwan/2645/2006 (H1N1)
HLA-B8 HLA-B*0801	380–388	ELRSRYWAI	A/New Caledonia/20/1999 (H1N1) A/Taiwan/2645/2006 (H1N1) A/Managua/107.01/2008 (H1N1) A/Florida/UR07-0026/2008 (H1N1)

*HA, hemagglutinin; NP, nucleoprotein; MHC, major histocompatibility complex; NA, neuraminidase. Epitope binding to and/or activation of specific lymphocytes prepared from human peripheral blood mononuclear cells (PBMC): MHC-tetramer staining; T-cell receptor binding; ELISPOT and intracellular cytokine staining (interferon γ), and/or ^{51}Chromine release and killing have been demonstrated in published studies. Data on epitope characterization were collected from the Immune Epitope Database (IEDB; www.immuneepitope.org) (*4*).

In fact, although there are no experiments establishing a solid link, cross-reactive immunity from seasonal influenz or vaccination may result in partial protection of patients infected with influenza virus (H5N1). As reported by WHO for influenza virus (H5N1)–infected patients, the incidence of reported infections was lower for those ≥40 years of age (22/202, 10.9%) than for those <39 years of age (180/202, 89.1%), and the fatality rate was 32% (7/22) for those ≥40 years of age and 59% (106/180) for those <40 years of age from 2003 to 2006 (www.who.int/wer/wer8126.pdf). Therefore, repeated exposure to seasonal influenza viruses or vaccination may have resulted in partial cell-mediated or humoral immunity to influenza virus (H5N1). The same type of immunity may have happened in persons exposed to pandemic (H1N1) 2009 virus as well.

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Serologic Survey of Pandemic (H1N1) 2009 Virus, Guangxi Province, China

To the Editor: Since mid-April 2009, a new influenza A virus (H1N1), now called pandemic (H1N1) 2009 virus, has caused influenza outbreaks in humans in North America (*1*) and a worldwide pandemic (*2*–*4*). Human pandemics occur when a new virus subtype emerges that is capable of human-to-human transmission in a population with little or no neutralizing antibodies to the new virus (*4*).

The current outbreak presents the first opportunity to directly observe this process. We used hemagglutination inhibition (HI) and virus neutralization (VN) assays to detect antibodies in 4,043 serum samples from residents (7–84 years of age) of 2 counties in Guangxi Province, People's Republic of China, collected during July–August 2008. These persons were mostly farmers who lived in rural areas. Serum samples were obtained, transported, and frozen at –80°C as described (*5*). No participants had a history of vaccination against seasonal influenza. Antibodies were also detected in another 22 persons (<40 years of age) in Shantou, Guangdong Province, who had received 3 vaccinations for seasonal influenza since 2006.

Influenza viruses used in this study were A/California/04/2009 (H1N1; CA04), A/Brisbane/59/2007 (H1N1; B59), and A/swine/Hong Kong/915/2004 (H1N2; Sw915). CA04 and B59 were kindly provided by the World Health Organization Collaborating Centers for Reference and Research on Influenza (Atlanta, GA, USA, and Parkville, Victoria, Australia). Sw915 was isolated from pigs by our laboratory. Seven of 8 genomic segments of Sw915 were located in a sister lineage to the current outbreak; this strain is the most closely related swine virus to CA04 identified to date (*6*). All serum samples were treated with a receptor-destroying enzyme and absorbed with fresh turkey erythrocytes to remove nonspecific inhibitors before the assays. All samples were tested by HI and VN assays according to standard protocols (*5*).

Screening by HI assay showed that 70 samples were positive (titers ≥40) for CA04 (Table). Examination by VN assay showed that of 70 HI-positive serum samples, 12 had detectable neutralizing antibodies to CA04 (positive rate 0.3%). Of these VN-positive samples, 10 had titers of 40–80 and only 2 had neutralizing antibody titers ≥160 (Table). The 12 persons from whom the samples were obtained were 30–60 years of age. In contrast with findings from a recent serologic survey of a US population (*7*), our results showed that none of the 583 persons ≥60 years of age in our study was VN seropositive for CA04.

All 70 HI-positive samples for CA04 were also screened for neutralizing antibodies against Sw915. Thirteen samples collected from persons 40–84 years of age were VN positive (titers 40–160). Of these 13 samples, 5 were positive (VN titer ≥40) for CA04 and 8 were negative. However, 7 CA04 VN-positive samples were negative for Sw915. These findings suggest that some cross-reactivity exists between CA04 and other Sw915-like H1 subtype viruses circulating in the pig population in southern China, and that sporadic human infection with H1 swine viruses has occurred in rural China, where exposure to pigs is common.

In contrast, screening all 4,043 serum samples with A/Brisbane/59/2007 showed that 159 (3.9%) samples had HI titers ≥40, of which 116 (2.9%) had neutralizing antibodies (titer ≥40) (Table). Only 3 serum samples from persons >60 years of age were VN positive for B59. Because the study group was not vaccinated, these results likely reflect natural infection rates for seasonal influenza virus (H1N1). The

Table. Serum antibodies to pandemic (H1N1) 2009 virus A/California/04/2009 and influenza A virus (H1N1) A/Brisbane/59/2007 in unvaccinated and vaccinated persons, Guangxi Province, People's Republic of China*

	No. (%) unvaccinated persons, n = 4,043		No. (%) vaccinated† persons, n = 22	
Virus, titer	HI	VN	HI	VN
Pandemic (H1N1) 2009 virus A/California/04/2009				
40–80	64	10	0	0
≥160	6	2	0	0
Total	70 (1.7)	12 (0.3)	0	0
Influenza A virus (H1N1) A/Brisbane/59/2007				
40–80	131	64	9	9
≥160	28	52	10	11
Total	159 (3.9)	116 (2.9)	19 (86)	20 (91)

*HI, hemagglutination inhibition; VN, virus neutralization.
†Persons were vaccinated starting in 2006 with influenza virus (H1N1) strains A/New Caledonia/20/1999, A/Solomon Islands/3/2006, and A/Brisbane/59/2007.

22 serum samples from vaccinated persons had no neutralizing antibodies against CA04, but all had high seroconversion rates for B59 (Table).

Our results suggest that most persons in our study population from Guangxi, China, are seronegative for pandemic (H1N1) 2009 virus (*1*). Serum samples from only 0.3% of persons tested neutralized the novel CA/04 strain. This finding contrasts with findings from the United States that serum samples from ≈11% of unvaccinated persons had antibodies against CA04 (*7*). Furthermore, all CA04-positive persons in our study were ≤60 years of age; the US study reported a 33% seropositive rate for this age group.

These differences may have been caused by the high proportion of seasonal influenza vaccination coverage in the United States when compared with results form our unvaccinated population from southern China. Therefore, we suggest that vaccination against seasonal influenza, rather than exposure to older, seasonal, influenza viruses (H1N1), which may be genetically and antigentically similar to pandemic (H1N1) 2009 virus, as suggested (*7*), might have generated partial protection against this new virus. No persons in our vaccinated control group had neutralizing antibodies against CA04.

We hypothesize that the absence of neutralizing antibodies in our control group, all of whom had been vaccinated 3 times, suggests that prolonged and repeated vaccination is required for partial immunity to CA04 or that older vaccines may confer some degree of protection. If these serologic differences are indicative of increased susceptibility, we would expect higher infection attack rates in largely unvaccinated populations than in vaccinated populations in countries such as China.

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Antiviral Drugs for Treatment of Patients Infected with Pandemic (H1N1) 2009 Virus

To the Editor: The emergence of influenza A pandemic (H1N1) 2009 virus in North America and associated illness and death suggest that humanity faces a dangerous threat. Viruses isolated from a sample of patients with confirmed cases in early phases of the outbreak demonstrated resistance to amantadine and rimantadine. At present, circulating viruses appear to be largely susceptible to the neuraminidase inhibitors oseltamivir and zanamivir, although oseltamivir resistance has been observed in recent cases in Europe, Asia, and North America (*1*). More recently, pandemic (H1N1) 2009 virus resistance to oseltamivir emerged during treatment of 2 immunosuppressed patients in the United States. Such cases demonstrate that oseltamivir resistance can emerge in infected persons treated with oseltamivir. To date, all isolates tested have been susceptible to zanamivir.

Vaccines are being deployed in some well-resourced countries but are generally not available to the public. It appears that little if any protection is offered from previous seasonal influenza vaccines. In the spring of 1918, epidemiologic observations indicated the likely emergence and spread of another influenza virus (H1N1) that caused few deaths. However, later that year, transmission resurged and was associated in 2 waves with increased illness and deaths. We cannot predict whether the 2009 pathogen will follow a similar temporal pattern and evolve toward increased virulence. Even if vaccine development and delivery could be achieved within 6 months, an aggressive schedule, large supplies of vaccine against pandemic (H1N1) 2009 may not be available until late 2009.

Antiviral drugs are used to treat patients with strongly suspected or confirmed influenza. However, until a vaccine is available, specific protection by pharmaceutical products is limited to antiviral drugs. Nonpharmaceutical interventions are also available for prevention. Some governments and organizations are taking steps that would enable mass administration of these drugs (*2*). This administration may prove problematic. A recent study showed that schoolchildren may incompletely adhere to oseltamivir prophylaxis instructions (*3*). If other groups are given oseltamivir prophylaxis, they cannot necessarily be expected to follow administration guidelines; compliance with taking the recommended number of doses at appropriate times is difficult to enforce. Moreover, even when compliance is high, oseltamivir prophylaxis may fail (*4*).

The first viable oseltamivir-resistant human influenza viruses (H1N1) emerged and became prevalent in the United States and Europe in the 2007–08 influenza season, and prevalence of such viruses has continued in 2009. The potential for overuse of antiviral drugs, especially oseltamivir, to select for existing antiviral drug-resistant strains is unknown. Ecologic studies suggest a lack of association between prevalence of oseltamivir use and prevalence of oseltamivir resistance (*5*). However, examination of seasonal influenza virus isolates obtained before introduction of oseltamivir showed an absence of resistance (*6*), leading some to conclude that antiviral monotherapy leads to selection pressure for resistance (*7*). Regardless of origin of resistance, recent seasonal influenza viruses (H1N1) of the A/Brisbane/57/2007 lineage from around the world display such resistance.

A similar resistance pattern could occur with pandemic (H1N1) 2009 virus. Regardless of the mutational mechanism for antiviral drug resistance, mass use of antiviral drugs could potentially lead to selection pressure for drug-resistant viruses (*7*). Experience with seasonal influenza demonstrated the fitness of some oseltamivir-resistant strains (*8*). Moreover, modeling studies suggest that antiviral-resistant strains may spread rapidly and markedly affect pandemic outcomes (*9*).

What are we to do? Until a vaccine is available, combination antiviral therapy and rapid diagnostic testing may be needed (*7*). Given the recently described low sensitivity of currently available rapid tests, applying such assays to all patients is problematic (*10*). If rapid testing has a role, it should be used in testing persons at highest risk for developing influenza complications. However, early empiric therapy based on clinical manifestations and knowledge of circulating strains is likely more appropriate than reliance on tests with low sensitivity. Updated guidelines recently issued by the World Health Organization (www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf) and the Centers for Disease Control and Prevention (www.cdc.gov/h1n1flu/recommendations.htm) for prophylaxis should be followed to keep resistance in check and save the lives of patients.

A widely administered protective vaccine is needed to prevent transmission and infection and preserve the efficacy of antiviral agents. Indiscriminant administration of these agents could support proliferation of antiviral resistance in pandemic (H1N1) 2009 virus or an evolved variant. Appropriate use of antiviral chemotherapy is complex. Identifying the groups at high risk for serious illness for drug therapy and appropriate antiviral therapy in situations of co-circulation of seasonal and pandemic (H1N1) viruses with various susceptibility patterns needs elucidation. Without clear evidence-based guidance, a global public health disaster could occur if pandemic (H1N1) 2009 reemerges

later this year with higher virulence or widespread antiviral drug resistance.

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Imported Ciprofloxacin-Resistant *Neisseria meningitidis*

To the Editor: Emergence and spread of antimicrobial drug resistance in community-acquired infections is a global threat. Resistance of *Neisseria meningitidis* raises concern because of severity of disease caused by this organism and the need for immediate treatment of infected patients.

We report an imported case of meningococcal disease caused by fluoroquinolone-resistant *N. meningitidis*. The patient, a previously healthy, unvaccinated 43-year-old man who had traveled internationally, was hospitalized because of high fever, neck stiffness, and a diffuse petechial rash Signs and symptoms were observed 24 hours after he had returned to Italy from a 10-day business trip during February–March 2009, to New Delhi and Chennai in India and a stopover of a few hours in Frankfurt, Germany.

Microscopic examination of cerebrospinal fluid showed gram-negative diplococci and culture documented *N. meningitidis* serogroup A. The strain was characterized as serotype 4,21 subtype P1.9 by using monoclonal antibodies. Multilocus sequence typing performed at the National Reference Laboratory for Invasive Meningococcal Diseases in Rome characterized the strain as sequence type (ST)-4789 and belonging to clonal complex ST-5/subgroup III.

Antimicrobial drug susceptibility was determined by using an agar dilution test, and MICs were determined by using an agar disk-diffusion test (Etest; AB Biodisk, Solna, Sweden) and standard techniques. The strain was resistant to ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole and susceptible to penicillin, ampicillin, ceftriaxone, chloramphenicol, rifampin, and azithromycin. MICs for ciprofloxacin, levofloxacin, penicillin, ampicillin, and ceftriaxone were 0.25, 0.25, 0.03, 0.12, and <0.016 mg/L, respectively (Figure). The patient recovered after treatment with ceftriaxone.

Before results of antimicrobial drug–susceptibility testing were available, 15 adult contacts of the patient received ciprofloxacin as chemoprophylaxis according to public health recommendations in Italy. After positive test results, all contacts were offered repeat chemoprophylaxis with rifampin; 13 of them accepted. A diagnosis of meningitis and results of antibiograms were sent to the patient's place of employment in India and to the airport manager in Frankfurt. However, we were not able to assess what chemoprophylaxis was given to the patient's fellow employees and air travel contacts. No secondary cases have been detected so far in Italy.

Sporadic cases of infection with *N. meningitidis* (mainly serogroup B) with reduced susceptibility to ciprofloxacin have been reported in Europe, North and South America, and Australia since 2000 (*1–4*). Ciprofloxacin-resistant *N. meningitidis* of serogroup A caused an outbreak of meningococcal meningitis in Delhi, India, in 2005 and a recurrence in 2006 (*5*). Although the patient reported in our study had no known contact in India with patients who had meningococcal disease, mul-

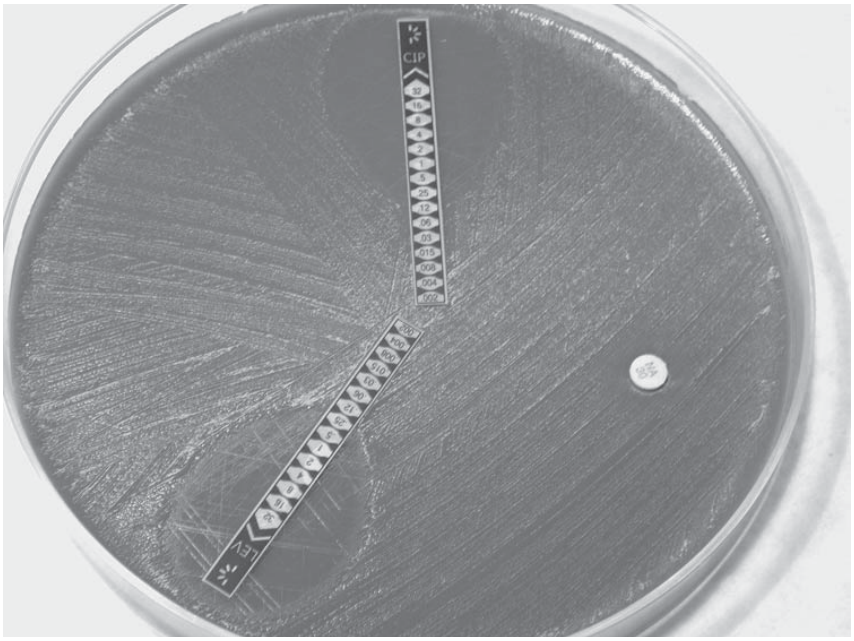

Figure. Antimicrobial drug–susceptibility test, showing resistance to levofloxacin (LEV, lower strip), ciprofloxacin (CIP, upper strip), and nalidixic acid (NA, disk) for the strain of *Neisseria meningitidis* isolated from the patient. A color version of this figure is available online (www.cdc.gov/EID/content/15/11/1852-F.htm).

tilocus sequencing typing analysis showed that the isolate had the same sequence type as isolates from the epidemic in India (*5*,*6*).

We report isolation of an imported, ciprofloxacin-resistant strain of *N. meningitidis* isolated from a patient with meningococcal disease. During the past 2 years, 182 strains of *N. meningitidis* have been sent to the Istituto Superiore di Sanità; all were susceptible to ciprofloxacin and MICs ranged from 0.002 mg/L to 0.006 mg/L (National Reference Laboratory for Invasive Meningococcal Diseases, pers. comm.) Serogroup A *N. meningitidis* accounted for only 1 of these strains; serogroups B and C are the most common groups in Italy. In contrast, group A meningococci are the major cause of meningitis outbreaks worldwide, especially in Africa and Asia. To date, spread of ciprofloxacin resistance in serogroup A appears to be limited to India because a recent report of antimicrobial drug susceptibility of *N. meningitidis* in the meningitis belt of Africa during 2000–2006 showed no evidence of ciprofloxacin resistance (*7*).

Temporal correlation and epidemiologic features strongly suggest that transmission of *N. meningitidis* to our patient occurred during his journey to India. Meningococcal disease is rarely imported because onset of symptoms is often rapid and severe. Nonetheless, the enormous increase in global trade and travel and shortening of international travel time may increase the risk for spread of infectious diseases and drug-resistant organisms. In addition, carriage of *N. meningitidis* in the nasopharynx of otherwise healthy persons can occur.

Emergence of fluoroquinolone resistance in some countries raises concerns about current chemoprophylaxis recommendations for meningococcal disease. Ciprofloxacin is widely used for postexposure prophylaxis of close contacts of infected persons because it is simple to use (single oral dose) and lacks toxicity. However, patients and their contacts should be questioned about possible recent travel. When transmission of *N. meningitidis* is suspected in regions where fluoroquinolone resistance has been found (New Delhi, India, and North Dakota and western Minnesota in the United States), alternative chemoprophylaxis such as rifampin or ceftriaxone should be used.

Emergence of autochthonous ciprofloxacin-resistant *N. meningitidis* is possible in countries where fluoroquinolones are widely used. In vitro drug susceptibility testing is not routinely and uniformly used in all settings because treatment or chemoprophylaxis are usually started before antibiogram results are available. Our case demonstrates that drug susceptibility testing should be encouraged and routinely performed for all isolates. Local and worldwide surveillance for antimicrobial drug–resistant *N. meningitidis* is crucial for determining antimicrobial drug resistance trends and future recommendations for chemoprophylaxis and treatment.

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Letters

Letters commenting on recent articles as well as letters reporting cases, outbreaks, or original research are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have 1 Figure or Table and should not be divided into sections. All letters should contain material not previously published and include a word count.

Imported Chikungunya Virus Strains, Taiwan, 2006–2009

To the Editor: Chikungunya is a reemerging infectious disease that is endemic to Africa and Asia and caused by a mosquito-borne alphavirus in the family *Togaviridae*. Previous phylogenetic studies showed that chikungunya virus (CHIKV) strains were clustered into 3 distinct genotypes separated primarily by location into West African, Central/East/South African, and Asian genotypes (*1*,*2*).

Earlier outbreaks in Thailand, Cambodia, Vietnam, Myanmar, the Philippines, Malaysia, Indonesia, Pakistan, and India during 1960–1999 were caused by strains of the Asian genotype (*2*). However, explosive epidemics in Indian Ocean islands and India since 2005 and the worldwide increase in travel have changed the distribution of CHIKV genotypes. Recent studies have shown that different lineages of CHIKV strains of the Central/East/South African genotype have expanded locally and spread to new areas in Africa, Europe, and Asia and caused epidemics (*2*–*7*).

Imported chikungunya cases were identified at airports by active surveillance (fever screening) in Taiwan (*3*). Among 14,289 febrile patients arriving at Taiwan Taoyuan International Airport from January 2006 through February 2009, a total of 13 were confirmed to have CHIKV infections. One additional chikungunya case was detected at Kaohsiung International Airport among 801 febrile patients from February 2008 through February 2009. These imported cases were introduced from Indonesia (7 cases), Malaysia (4 cases), Singapore (1 case), Bangladesh (1 case), and India (1 case). Real-time quantitative reverse transcription–PCR showed virus titers ranged from $10^{3.6}$ PFU/mL to $10^{6.4}$ PFU/mL for day 1–3 acute-phase serum samples from these patients. CHIKV strains were successfully isolated by using a cell culture (C6/36) method (online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1854-Techapp.pdf).

To identify genetic relationships among these 14 imported CHIKV isolates, complete structural polyprotein gene sequences of 10 isolates (GenBank accession nos. FJ807886–FJ807895) and full genome sequences of 4 isolates (Singapore/0611aTw, Indonesia/0706aTw, Bangladesh/0810aTw, and Malaysia/0810bTw strains) (GenBank accession nos. FJ807896–FJ807899) were determined. Nucleotide sequences of complete open reading frames of Singapore/0611aTw, Bangladesh/0810aTw, and Malaysia/0810bTw isolates were most closely related to the India IND-06-AP3 strain (99.95%, 99.84%, and 99.77% identities, respectively) and other India 2006 isolates, which suggests common genetic origins from India.

In comparison with other CHIKV strains, unique substitution K252Q in the envelope 2 (E2) protein was found in all 4 imported isolates from Malaysia, and 2 unique substitutions, V4A and N349D, in the envelope 1 (E1) protein were found in the imported Bangladesh/0810aTw isolate. The Indonesia/0706aTw isolate was most closely related to the Malaysia MY003IMR isolate (99.42% identity). A novel 4-aa deletion, corresponding to nonstructural protein 3 codons 379–382 (TTACCAACCATA coding for Leu-Pro-Thr-Ile in the Malaysia MY003IMR strain), was observed in the Indonesia/0706aTw strain when it was compared with other CHIKV sequences available in GenBank. Further sequence analysis showed that all 6 isolates from Indonesia had the same deletion in this region.

A phylogenetic tree based on 49 CHIKV partial E1 gene sequences was constructed to trace the origins of the 14 CHIKV strains reported in this study (Figure). Phylogenetic

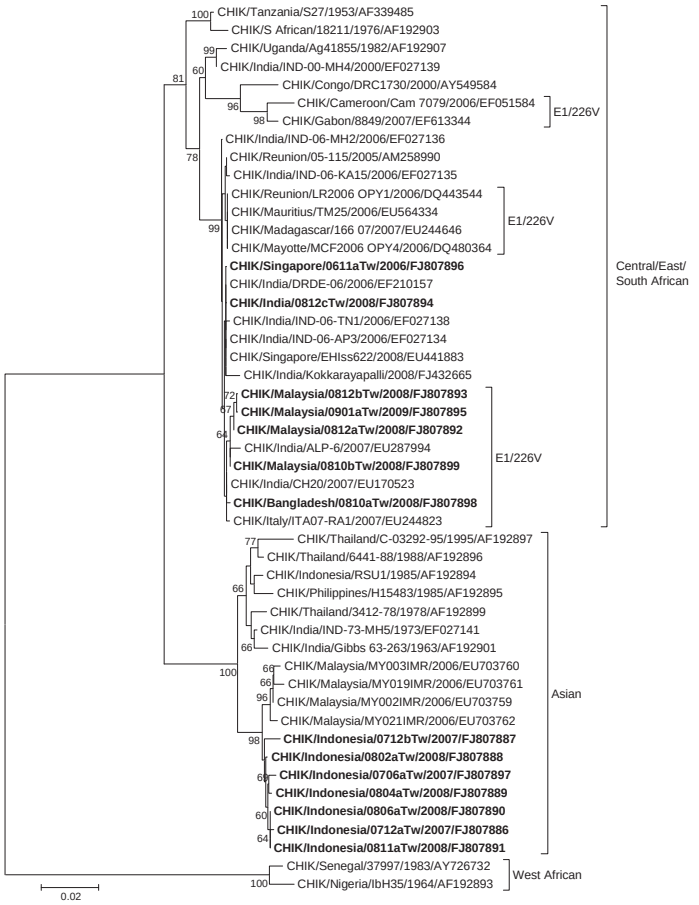

Figure. Phylogenetic relationships of chikungunya virus (CHIKV) isolates from 14 imported cases of chikungunya, Taiwan, 2006–2009. The tree was constructed on the basis of partial envelope 1 (E1) nucleotide sequences (836 bp, nt positions 10264–11099 of the prototype CHIKV S27 genomic sequence) of 49 CHIKV strains. Sequences obtained in this study are indicated in **boldface**. CHIKV strains with the E1-A226V mutation are indicated. Genotypes are indicated on the right. Viruses were identified by using the nomenclature of virus/country/strain/year of isolation/GenBank accession number. Analysis was performed by using MEGA 4 software and neighbor-joining (maximum composite likelihood) methods. Bootstrap support values >60 are shown (1,000 replicates). West African genotype Senegal strain 37997 sequence was used as the outgroup virus. Scale bar indicates nucleotide substitutions per site.

analysis shows that all 7 strains from Indonesia isolated during 2007–2008 are grouped into the Asian genotype and clustered in a distinct lineage. This lineage shows close relationship to the Malaysia/MY002IMR/2006 isolate. However, the 4 strains from Malaysia isolated during 2008–2009 belong to the Central/East/South African genotype and are clustered with CHIKV strains of India/ALP-6/2007, Italy/ITA07-RA1/2007, and Bangladesh/0810aTw/2008. These viruses also have the E1-A226V mutation. The imported Singapore/0611aTw/2006 and India/0812cTw/2008 strains belong to the Central/East/South African genotype and are clustered with several India/2006 (IND-06-AP3, IND-06-TN1 and DRDE-06), India/Kokkarayapalli/2008, and Singapore/EHIss622/2008 strains, which have an alanine at the position E1–226.

Our results provide insights into the current distribution of different CHIKV genotypes and lineages. Phylogenetic analysis demonstrated that CHIKV strains isolated from Indonesia during 2007–2008 remain stable and belong to the Asian genotype, whereas the other 7 isolates from Singapore, Bangladesh, Malaysia, and India belong to the Central/East/South African genotype. The Malaysia/2008–2009 and Bangladesh/2008 isolates have the E1–226(V) mutation similar to reported variants isolated in Cameroon, some Indian Ocean islands, India, Italy, and Gabon during 2006–2007 (*4*,*6*–*9*). These results show that different lineages of CHIKV strains from India with the Central/East/South African genotypes have been transmitted long distances by infected persons to various countries in Asia, including Singapore, Malaysia, and Bangladesh.

Although the urban mosquito *Aedes aegypti* is the primary vector for dengue and chikungunya transmission in Asia, the *Ae*. *albopictus* mosquito, a less efficient vector, was recently identified as the main or alternate vector in chikungunya outbreaks in central and East Africa (*4*,*7*,*10*), India (*8*), and Italy (*6*). Recent studies have suggested that the increased chikungunya outbreaks caused by CHIKV strains of the Central/East/South African genotype might be associated with a change in 1 nt, the A226V mutation, in the E1 protein during continuous epidemics (*8*,*9*). It is not known whether E1-A226V variants play a dominate role in urban or periurban areas of Asia and Africa where *Ae*. *aegypti* and *Ae*. *albopictus* mosquitoes are present.

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Cutaneous Larva Migrans Acquired in Brittany, France

To the Editor: Hookworm-related cutaneous larva migrans is a parasitic dermatosis caused by the penetration of larvae, mostly of a dog or cat hookworm, into the epidermis of humans (*1*,*2*). This eruption is most commonly found in tropical and subtropical areas but was recently reported from western Europe, including Germany (*3*,*4*), England (*5*,*6*), Scotland (*7*), and southern France (*8*). We report a patient from the Netherlands who acquired hookworm-related cutaneous larva migrans while on a holiday in Brittany, France.

A previously healthy 40-year-old man from the Netherlands traveled to Brittany, France, to visit from September 1 to September 15, 2008. He and his partner slept in tents, sometimes camping rough (not on designated camping sites or on private property), and they stayed in low-budget hotels. They spent a lot of time on several beaches along the Atlantic Ocean on the southern shore of Brittany (≈48°N). The weather during their stay was variable. The patient was frequently bitten by mosquitoes, especially on his feet. He had not traveled to the tropics before and did not own any pets.

After his return to the Netherlands, the area around 2 presumed mosquito bites at the lateral side of his right foot became red, swollen, and itchy. This area evolved into a 1-cm pustule that later turned into a bulla. On November 10, he visited his general practitioner, who made a diagnosis of cellulitis and started the patient on amoxicillin/clavulanic acid 625 mg, 3×/day for 10 days. During antimicrobial drug treatment, skin inflammation improved, but after 2 days the patient noticed that an itching red streak had developed, extending from the lesions on the lateral side of the right foot to the whole width of the sole of the foot. The tip of the streak proceeded along the sole of the foot at the rate of 2 cm/day. On the fifth day, he was referred to our Tropical Diseases outpatient clinic.

Physical examination showed 2 elevated, ulcerative lesions on the lateral side of the right foot, and from each originated an elevated serpiginous lesion (Figure, panels B and C). These were typical tortuous lesions 2 cm in width. One of the lesions ran across the whole sole of the right foot and was 14 cm in length (Figure, panels A and C). The medial end of the lesion was fervently erythematous. Based on clinical signs, we diagnosed the skin lesion as hookworm-related cutaneous larva migrans with secondary impetiginization. The patient was subsequently treated with a single oral dose of 12 mg ivermectin. The itch and the progression of the lesion halted instantly and the lesion disappeared during the following weeks. The larva was not extirpated and thus not further identified.

Hookworm-related cutaneous larva migrans is usually caused by *Ancylostoma brasiliense*, *A. caninum* or, rarely, *Uncinaria stenocephala*. These zoonotic hookworms need a high temperature and a moist environment to develop from an embryo to filariforme larva (*1*,*2*). Hookworm-related cutaneous larva migrans is typically a disorder of tropical and subtropical zones and it is rather common among tourists who visit tropical beaches. This was the first patient we had seen with this disease who became infected in west-

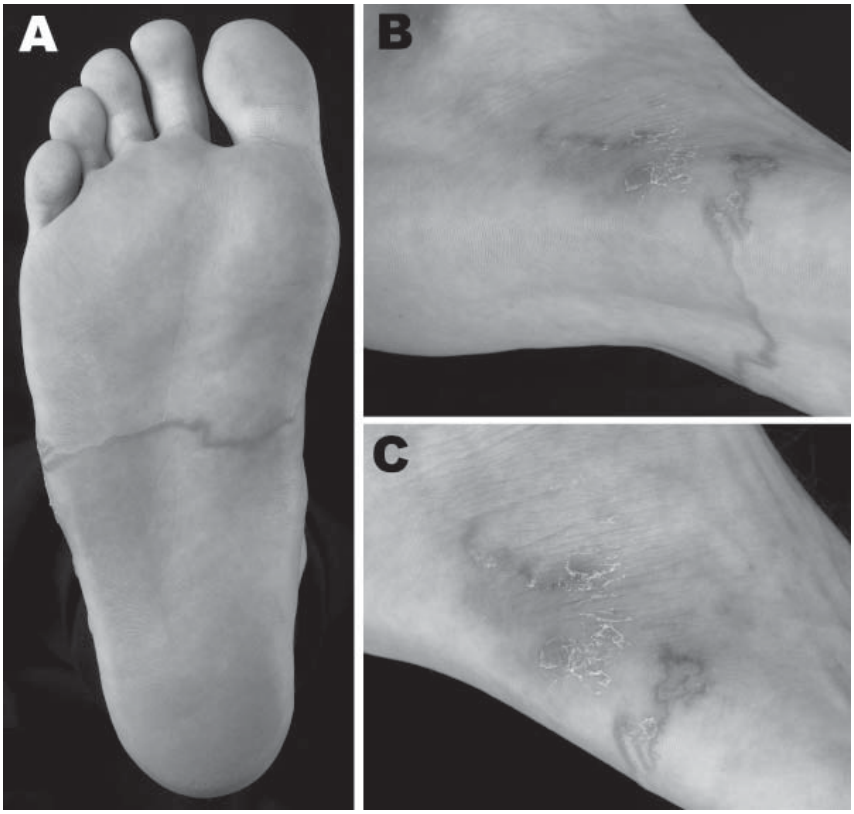

Figure. Right foot of a patient from Brittany, France, with a hookworm-related cutaneous larva migrans, showing an elevated serpiginous lesion on the sole of the foot (panels A, B) and ulcerative lesions at the origin of the lesions on the lateral side of the foot (panel C). A color version of this figure is available online (www.cdc.gov/EID/content/15/11/1856-F.htm).

ern Europe. Apart from an exceptionally hot day on August 30 (maximum 26°C), the weather was not particularly warm during the summer of 2008 in Brittany; during the first 2 weeks of September the average minimum and maximum temperatures were 11°C and 17°C, respectively. Rainfall was moderate and humidity was ≈86% (*9*). However, the overall warmer climate, including warmer winters, might have created the conditions for zoonotic hookworm infections in humans in western Europe (*10*).

Our patient may have been infected by *U. stenocephala*, a nematode of dogs that is common in temperate zones but rarely causes hookworm-related cutaneous larva migrans. An increase in ambient temperature might increase the incidence of these zoonotic infections in northern regions. Only 4 cases of hookworm-related cutaneous larva migrans were previously reported in France, all from southern regions (*8*). A northern spread of hookworm-related cutaneous larva migrans could thus point to expansion of the global distribution of the more tropical hookworms or altered conditions that favor the emergence of infection by a zoonotic hookworm such as *U. stenocephala*. Either explanation calls for screening of infection in cats and dogs and preventing pet animals and possibly stray animals from accessing beaches. Clinicians should be aware of the possibility of hookworm-related cutaneous larva migrans in patients who have traveled to western Europe and, in particular, those who have stayed on the beaches.

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European Perspective of 2-Person Rule for Biosafety Level 4 Laboratories

To the Editor: Recently, the directors of Biosafety Level 4 (BSL-4) laboratories in the United States published their views of the requirement of having ≥2 persons present at all times while biological work is undertaken in a BSL-4 laboratory (*1*). They concluded that safety and security would be better assured in some situations by video monitoring systems rather than by the presence of a fellow scientist. As members of the European Network of Biosafety Level-4 laboratories (Euronet-P4) who have developed guidelines in this area (*2*–*4*), we discussed the article during a recent network meeting. Biosafety and biosecurity are the major concerns for all involved in BSL-4 activities, and we support the authors' initiative and broadly agree with their position. The consensus among European BSL-4 experts is that, in the interest of safety, standard practice should be for all laboratories to perform a risk assessment before any activity is undertaken. This preliminary assessment is the best way to determine procedures to be used, including whether 2 persons should work together as part of laboratory procedure. A 2-person rule is inappropriate simply because the best approach is not to have inflexible rules that are not objectively assessed according to laboratory-specific circumstances.

Surveillance video monitoring and data storing have their place in protecting laboratory facilities from unauthorized access and theft of materials, but their effectiveness for ensuring proper handling of pathogens is quite limited. Finally, we agree with the authors that both biosafety and biosecurity must be founded on careful selection and monitoring of staff, without which even the most sophisticated of control systems would fail.

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Multidrug-Resistant *Mycobacterium tuberculosis* Strain from Equatorial Guinea Detected in Spain

To the Editor: Eleven years of molecular epidemiologic data allowed the Spanish Multidrug-resistant Tuberculosis (MDR TB) Surveillance Network to identify a specific MDR *Mycobacterium tuberculosis* strain that had been imported into Spain from Equatorial Guinea (*1*). Our study brings to light the potential dissemination of this strain (named MDR-TBEG) in Equatorial Guinea, a country where little is known about the extent and features of TB or MDR TB. It also highlights that MDR strains can spread across continents, and thus MDR TB's emergence in any country becomes a global problem.

Ten MDR *M. tuberculosis* isolates obtained from 10 patients from Equa-

torial Guinea were detected in Spain during 2000 through 2008. Evidence of clonality was found within the 10 isolates because all exhibited identical genetic profiles defined by different molecular epidemiology methods (*2*,*3*) and mutations involved in drug resistance (Figure). Notably, none of the remaining 504 MDR isolates in the Spanish database matched SIT177, a spoligotype belonging to the Latin American–Mediterranean 9 (LAM9) subfamily (*4*).

The data routinely collected for all cases of MDR TB have been previously described (*1*). All 10 patients in the study were from Equatorial Guinea, a small African country on the Gulf of Guinea with a population of ≈500,000, an MDR TB rate >2.0% (*5*) of all combined (new and previously treated) TB cases, and an estimated adult HIV prevalence rate of 3.2% (www.who.int/globalatlas/predefinedReports/EFS2008/full/EFS2008_GQ.pdf). The MDR TB isolates were collected within a 9-year period (online Technical Appendix, available from www.cdc.gov/EID/content/15/11/1858-Techapp.pdf): 1 in 2000, 2 in 2001, 3 in 2003, 1 in 2004, 2 in 2007, and 1 in 2008. According to their hospitals of origin, the patients were geographically dispersed in 6 different Spanish cities. We found that the interval between the patients' arrival in Spain to the initiation of anti-TB treatment was <3 months in 6 patients, 3 of whom were clinically ill at the time of arrival. Seven patients were adult men, 2 were adult women, and 1 was an 8-year-old girl. The patients' mean age was 30 years (range 8–54 years). Three patients were seropositive and 4 were seronegative for HIV infection (the HIV status of 3 patients was unknown). Data on prior anti-TB treatment was available for 7 case-patients, of whom only 1 had a history of antecedent TB chemotherapy. Altogether, 3 patients died before completing treatment, including 2 patients affected by miliary TB, 1 of whom was HIV-coinfected. The third patient who died was a student without a known history of immunosuppression or previous TB who had lived for 2 years in Spain. We could not establish any epidemiologic links between these patients during their stay in Spain.

Analysis of drug resistance genes showed that all isolates harbored the *inhA* promoter mutation –15C→T (*6*). Alterations in the *inhA* gene were previously reported in 80% of the isoniazid-resistant isolates from Equatorial Guinea (*5*). Notably, a double mutation in the *rpoB* gene affecting codons 531 (Ser531Leu) and 561 (Ile561Val) was detected in the 10 MDR isolates. The presence of this uncommon mutation, Ile561Val, outside the rifampin resistance–determining region supports the hypothesis that the MDR isolates are clonal in origin. Furthermore, we demonstrated the absence of Ile561Val mutation in 3 drug-susceptible *M. tuberculosis* strains with an SIT177-LAM 9 spoligotype pattern, which ruled out a relationship between this spoligotype and the Ile561Val mutation.

Further analysis with phylogenetic markers assigned MDR-TBEG to the principal genetic group 2, the Euro-American lineage of *M. tuberculosis* and its West African sublineage, on the basis of polymorphisms in codons *kat*G463 and *gyr*A95, the 7-bp pks15/1 deletion, and RD174 (*7*,*8*), respectively. The analysis of the RD^{Rio} deletion confirmed that the strain belongs to the major RD^{Rio} sublineage of the LAM *M. tuberculosis* spoligotype family (*9*). This sublineage is a major cause of TB in Rio de Janeiro (Brazil) but has disseminated globally. Additional information on the geographic distribution of SIT177-LAM 9 was obtained from the updated International Spoligotyping Database (SITVIT2) of the Institut Pasteur de Guadeloupe. SITVIT2 (consulted on 23 July 2008) contained 57 isolates belonging to SIT177. Almost 50% (n = 28) came from Brazil, and 14% from Africa (Morocco, n = 6; Senegal, n = 2). The remaining isolates with known countries of origin (n = 9) were distributed in other unrelated countries. These data indicate that this particular spoligotype pattern is widely distributed.

We identified 1 MDR strain of *M. tuberculosis* RD^{Rio} sublineage isolated in Spain from Equatorial Guinean patients. Although the transmission of MDR-TBEG in Spain could not be conclusively ruled out, the fact that MDR TB developed in most patients

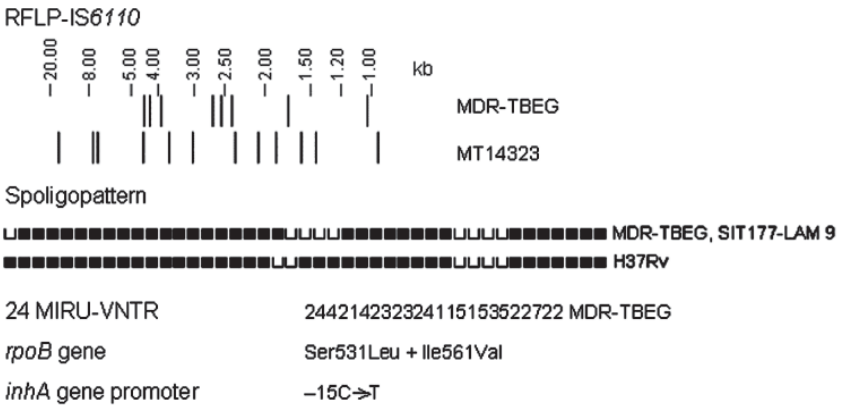

Figure. Genetic profile of the multidrug-resistant tuberculosis Equatorial Guinea strain (MDR-TBEG). RFLP, restriction fragment length polymorphism; SIT, spoligotype international type; LAM, Latin American-Mediterranean; MIRU-VNTR, mycobacterial interspersed repetitive-unit variable-number tandem-repeat. MIRU-VNTR loci order: MIRU 02, VNTR 42, VNTR 43, MIRU 04, MIRU 40, MIRU 10, MIRU 16, 1955, MIRU 20, QUB-11b, ETRA, VNTR 46, VNTR 47, VNTR 48, MIRU 23, MIRU 24, MIRU 26, MIRU 27, VNTR 49, MIRU 31, VNTR 52, QUB-26, VNTR 53, MIRU 39.

within 3 months after their arrival, as well as the spatiotemporal distribution of the MDR TB cases and its clonal origin, strongly suggest that MDR-TBEG was imported into Spain and that active transmission of this particular clone could be occurring in Equatorial Guinea. However, additional molecular and epidemiologic studies should be conducted in this sub-Saharan country to ascertain its role in recent transmission of MDR TB. Greater international efforts should be made to provide appropriate tools to resource-limited areas for fighting against MDR TB and preventing development of extensively drug-resistant TB.

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Hajj Pilgrims' Knowledge about Acute Respiratory Infections

To the Editor: Hajj pilgrimage is a yearly event in which >2 million Muslims from around the world gather in Mecca, Saudi Arabia. Such high density of crowding presents a risk for local outbreaks and for worldwide spread of infectious agents. Acute respiratory infection (ARI) is the leading cause of admission to Saudi hospitals during the Hajj (*1*). In Marseille, France, after administration of systematic questionnaires, we recorded attack rates of ARI up to 60% in cohorts of returned Hajj pilgrims in 2006 (*2*). This potential risk is of particular concern because of the influenza A pandemic (H1N1) 2009 virus (*3*). ARI transmission can be efficiently reduced by simple, low-cost physical measures, including use of face masks and hand hygiene. Awareness and acceptability of these measures among pilgrims, however, are limited (*4*).

We conducted a knowledge, attitudes, and practices survey that addressed these issues among Hajj pilgrims departing from Marseille during October and November 2008, several months before the outbreak of pandemic (H1N1) 2009 virus. A total of 528 persons (290 males, 238 females) who attended a pre-Hajj meningococcal vaccination campaign were invited to participate in a face-to-face interview during which they completed our questionnaire. We achieved a 100% response rate. Mean age of participants was 61 years (range 18–94 years). Most pilgrims were born in North Africa (92%), had education above a primary certificate (81%), were unemployed (56% of persons <65 years of age), and were traveling to Saudi Arabia for the first time (78%). Ten percent had chronic pulmonary disease.

We assessed knowledge of ARI using 18 questions about symptoms and sources of contamination. Knowledge questions were scored 1 for the correct answer and 0 for incorrect or "don't know" answers. Overall, the score of true responses was only 26% (interquartile range [IQR] 21%–37%). Scores were higher for respondents <65 years of age (32% [IQR 21%–42%] vs. 26% [IQR 16%–32%], $p<0.00001$ by Kruskal-Wallis test). Scores were also higher for female pilgrims (32% [IQR 21%–37%] vs. 26% [IQR 21%–37%, $p = 0.01$). No other demographic or health factor had significant influence.

Respondents believed the following were sources of contamination for ARI: sneeze and cough products (58.1%), dirty hands (43.9%), contact with ill persons (40.5%), saliva (17.2%), promiscuity (17.0%), food (12.1%), drink (9.1%), air conditioning (3.4%), and contact with animals (0.4%); 16.7% had no knowledge about ARI sources. When asked about their perceived risk of acquiring ARI during the pilgrimage and contaminating their relatives on returning home, 26% of respondents perceived no or little risk, 20% perceived some risk, and 37% perceived important risk; 17% did not know. Surveyed pilgrims knew the following were symptoms of ARI: cough (64.4% of respondents), dyspnea (45.1%), fatigue (33.3%); expectoration (21.0%), fever (15.2%), rhinitis (8.7%), nasal obstruction (4.0%), and headache and sneeze (3.8% each); 14.4% of pilgrims surveyed did not know any ARI symptoms. Less than 50% of respondents were aware of social distancing, curative treatment, and use of a face mask as precautions to reduce the spread of ARI agents (Table). However, when informed about the effectiveness of those prevention measures, most pilgrims were willing to wear a mask (92%), frequently wash their hands (98%), use hand disinfectants (89%), and use disposable handkerchiefs (97%) (Table).

Saudi health authorities recommend use of surgical face masks (*5*); however, data conflict about the protective effect of such masks during the pilgrimage (*5*,*6*). Use of face masks varies according to the origin of Hajj pilgrims; in 1 study, only 15% of pilgrims from the Middle East, 17% from Europe and the United States, and 45% from Southeast Asia used a mask (*4*). Promotion and distribution of free masks increased their use from 34% to 81% in another cohort of Saudi pilgrims (*6*). National Health Service for England does not advise

Table. Knowledge and acceptability of precautions against acute respiratory tract infections in French Hajj pilgrims, October–November 2008

Precaution	Knowledge about prevention measure		Acceptability of prevention measure, %
	Use for self-protection, %	Use for community protection, %	
Use of face mask	41.3	24.6	91.7
Hand washing	9.8	6.4	92.8
Use of hand disinfectant	2.8	1.9	98.1
Use of disposable handkerchief	–	1.1	96.8
Social distancing	48.7	57.4	62.5
Contact avoidance	47.0	54.7	62.1
Preventive treatment	14.6	–	–
Preventive vaccination	16.9	–	94.7
Curative treatment	–	46.2	97.7
No idea	11.2	7.8	–

the use of masks, considering compliance with this advice unlikely because many Muslims believe that covering the face during the Hajj is prohibited and because masks need to be of high quality and changed at least every 6 hours to remain effective (*7*). Recent studies demonstrated that surgical and N95 masks were equally effective in preventing spread of PCR-detectable influenza virus when used by infected patients. These masks also were potentially effective at preventing respiratory virus acquisition by household contacts of infected persons when worn by healthy persons. However, effectiveness depended largely on adherence to mask use (*8*,*9*).

Maintenance of good hand hygiene is also effective in reducing spread of respiratory infection. The World Muslim League has issued a *fatwa* allowing use of alcohol-based hand-rubs on skin as a disinfectant (*10*).

The demonstration of high acceptability of simple physical measures to prevent ARI encourages the education of pilgrims during the pretravel encounter. The results also support conclusion that masks, hand-rubs, and disposable handkerchiefs should be provided to pilgrims, along with strong advice about the risk for ARI, to increase adherence to prevention measures.

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Persistent Extended-Spectrum β-Lactamase Urinary Tract Infection

To the Editor: Uncomplicated urinary tract infections (UTIs) in otherwise healthy adults are usually treated empirically because the causative microbe is highly predictable: 80%–90% are caused by *Escherichia coli*. In addition, short courses of therapy (1 day or 3 days) are usually completed before laboratory results become available. In the past decade, reports of community-acquired, extended-spectrum β-lactamase (ESBL)–producing *E. coli* isolates have increased worldwide, but they are still uncommon in the United States (*1*), where reported cases are generally associated with hospitals. An early report of true community-acquired ESBL-producing *E. coli* infections in the United States was published in 2007 (*2*). We report a case of community-acquired lower UTI caused by ESBL-producing and multidrug resistant *E. coli* in an otherwise healthy college-aged woman who had no hospital exposure. Despite proper treatment, her infection persisted subclinically and symptoms recurred 2 months later.

The patient was an afebrile 24-year-old female college student who had visited her university health service, where she was recruited into a clinical trial investigating the effects of cranberry juice on UTIs. Inclusion in the study required that participants have UTI signs and symptoms, positive urine culture, and physician diagnosis. Participants provided self-collected vaginal, rectal, and midstream urine specimens at the time of enrollment and at 3- and 6-month follow-up or UTI recurrence. Study protocol was approved by the University of Michigan Institutional Review Board.

E. coli was isolated from all specimens collected from the patient

at the time of enrollment; urinalysis confirmed pyuria (>100 leukocytes/high power field). Also at the time of enrollment, the patient reported no antimicrobial drug treatment during the previous 4 weeks, no history of hospitalization, no urethral catheterization, and no sexually transmitted infection (confirmed by medical record review). A 7-day regimen of nitrofurantoin was prescribed.

After 53 days, the patient returned to the health service with recurring UTI symptoms and was treated with a 3-day regimen of trimethoprim–sulfamethoxazole; no urine specimen was submitted at that time. However, *E. coli* isolates were recovered from recurrence urine and rectal specimens collected within 48 hours according to the clinical trial protocol. All *E. coli* isolates collected at the time of enrollment (n = 3) and recurrence (n = 2) appeared morphologically and phenotypically identical (API Rapid 20E; bioMérieux, Durham, NC, USA). Genotyping using enterobacterial repetitive intergenic consensus (ERIC) PCR with an ERIC-2 primer showed a shared ERIC type, indicating identity (Figure). When tested for antimicrobial drug susceptibility (Vitek 2; bioMérieux), all 5 isolates were identified as ESBL-producers and were resistant to β-lactams: ampicillin, cefazolin, ceftriaxone (MIC >64 μg/mL), aztreonam, and piperacillin. After an ESBL confirmatory test, recommended by the Clinical and Laboratory Standards Institute (*3*), showed positive results, the isolates were also considered resistant to ceftazidime (MIC 1–4 μg/mL) and cefepime. Disk diffusion indicated susceptibility to cefoxitin. The isolates were also resistant to fluoroquinolones, tetracycline, and trimethoprim–sulfamethoxazole but susceptible to aminoglycosides, carbapenems, and nitrofurantoin. Isolates from the time of enrollment had intermediate susceptibility to amoxicillin–clavulanate (MIC 16 μg/mL), but isolates from the recurrence episode were resistant (MIC 32 μg/mL).

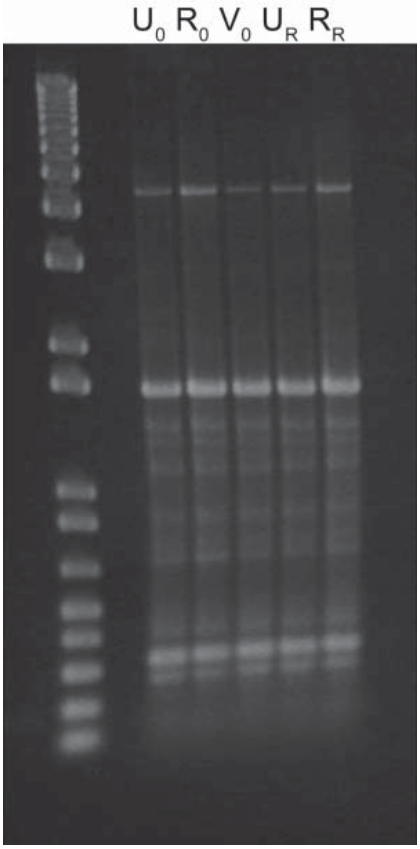

Figure. Enterobacterial repetitive intergenic consensus typing of extended-spectrum β-lactamase–producing *Escherichia coli* isolated from index ($_0$) and recurring ($_R$) urine (U), rectal (R), and vaginal (V) samples from a nonpregnant young woman.

Although the patient's initial UTI was treated adequately with nitrofurantoin, the infection recurred, implying that it remained in a reservoir, not uncommon for uncomplicated UTIs (*4*,*5*). Alternative antimicrobial drug treatment for outpatients with ESBL-producing *Enterobacteriaceae* is limited. Carbapenems remain the most effective drugs (*6*) but must be administered intravenously or intramuscularly (*3*). The reported efficacy of fosfomycin (*7*) suggests an option, but because agar dilution is the only recommended testing method, use of this drug in the United States is hindered. Use of antimicrobial drugs that concentrate in urine remains controversial as long as resistance is interpreted by MIC (blood-level resistance).

PCR detected β-lactamase resistance genes in all isolates, identifying them as ESBL positive when CTX-M consensus primer PCR was used but negative with TEM and SHV. Sequence analysis of the amplified gene showed that it encoded a CTX-M-15–like ESBL.

This isolate's increasing resistance to a β-lactamase–inhibitor combination, amoxicillin–clavulanate, suggested the possibility of inducible AmpC β-lactamase production. A negative AmpC disk test (with Tris/EDTA, cefoxitin, and *E. coli* ATCC 25922) refuted a plasmid-mediated AmpC β-lactamase (*6*); the remaining possible resistance mechanisms were hyperproduction of β-lactamase or an inhibitor-resistant penicillinase.

For the patient reported here, the multiple drug–resistant strain persisted for at least 53 days despite appropriate treatment with antimicrobial drugs. Furthermore, medical record review

found an additional UTI caused by *E. coli* 12 weeks later. Thus, because of the long duration of carriage of this highly resistant strain, potential for transmission to others is high.

The low number of previous reports of community-acquired ESBL in the United States does not necessarily suggest low community prevalence. Reports of ESBL-producer bacteremia in patients visiting emergency rooms suggests earlier and wider incidence (*8*). Returning to the practice of regularly culturing urine samples is difficult to justify; however, without ongoing surveillance to detect and control ESBL resistance, prevalence can only be expected to rise.

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Leishmania killicki Imported from Tunisian Desert

To the Editor: In North Africa, cutaneous leishmaniasis (CL) is a widespread zoonosis transmitted by sandflies. In Tunisia, 3 *Leishmania* species are responsible for CL: *L. major, L. infantum*, and *L. killicki. L. major* causes 2,000–4,000 zoonotic CL infections each year. *L. infantum*, the usual agent of visceral leishmaniasis, may be implicated in sporadic CL in northern Tunisia (dermotropic strains coexist with viscerotropic strains of *L. infantum* in these areas). *L. killicki* was first described in the desert region of Tataouine, Tunisia, in 1986 (*1*) and is the agent of chronic CL. We report a case of chronic CL caused by *L. killicki,* imported to Europe by a woman who had traveled to Tunisia.

A 76-year-old woman, with no relevant medical history, sought treatment from a dermatologist in Grenoble, France, for a cutaneous lesion on her right arm. This lesion had appeared 2 months after she returned from a July 2007 trip to Tunisia, where she spent 2 weeks in the desert riding camels and sleeping under a tent. The cutaneous lesion was isolated, round, 10 mm in diameter, ulcerative, surrounded by inflammation, and painless; no lymphadenopathy was found. The patient had no lesions on her mucous membranes and no concomitant general signs or symptoms. Given the absence of substantial signs or symptoms, the patient had paid no particular attention to this lesion until it became secondarily infected with bacteria. The secondary infection resolved after treatment with antimicrobial drugs, but the lesion persisted and a diagnosis of CL, presumably caused by *L. major*, was suggested.

Histologic investigation of a skin scraping showed amastigotes of *Leishmania* spp., but no further identification was done at that time. No treatment was given because the lesion was isolated and on the arm and because *L. major* lesions frequently heal spontaneously. After 2 months, the lesion had not healed, and *Leishmania* amastigotes were still found in scrapings. After 8 months, the lesion became inflamed, and a skin scraping sample was sent to the National Reference Center of *Leishmania* in Montpellier, France. DNA was extracted, and *L. killicki* was identified by genotyping. Various therapeutic options were considered, but no clear treatment recommendations were found. Parenteral therapy (pentavalent antimonials, pentamidine isethionate, or amphotericin B) was

not used because of adverse effects of these drugs. Miltefosine, used for visceral leishmaniasis (*2*), was an option because it can be taken orally and is well tolerated: however, its effectiveness for CL has mostly been evaluated for South American forms of CL, and its effectiveness for other forms is still not clear (*3*). Given the patient's older age and the fact that lesion was isolated, intralesional treatment with meglumine antimoniate was initiated. After 9 weekly injections, the lesion disappeared (10 months after onset).

CL caused by *L. killicki* is called chronic CL because lesions persist for years, as opposed to CL caused by *L. major*, for which lesions usually resolve without treatment after a few months. *L. killicki* was first considered to appear sporadically in limited areas, but a recent study found new foci in southern Tunisia (partly overlapping an *L. major*–endemic area) (*4*,*5*) and in neighboring countries such as Algeria (*6*) and Libya (*7*). Depending on the identification method used (multilocus enzyme electrophoresis or multilocus microsatellite typing), *L. killicki* is considered to be either a separate species or a variety of *L. tropica* (*8*,*9*). Although fewer *L. killicki* cases have been reported (≤20 cases since 1986), *L. killicki* infections differ from *L. tropica* infections because transmission seems strictly zoonotic (versus mostly anthroponotic for *L. tropica*) and because the clinical signs seem to be restricted to a chronic cutaneous lesion resistant to standard treatment.

The case reported here highlights the effect of ecotourism on imported diseases; journeys that were previously considered adventurous (i.e., physically challenging) are now easily accessible to anyone, thanks to the operation of well-organized tours. When treating travelers, clinicians must be aware of the specific epidemiology of disease agents in the regions visited. This case also shows the difficulties encountered when selecting treatment for leishmaniasis because it is still considered a neglected tropical disease, and thus the development of effective and nontoxic drug treatments has not been a priority. Lastly, this case shows how travelers can potentially spread rare diseases. Reservoirs and vectors can also be imported to other regions as a result of urbanization, climate change, and exportations. These factors lead to changes in environmental conditions favorable to spread of anthroponotic *Leishmania* spp. (urbanization) or to the establishment of tropical and/or subtropical vector species (global warming), and *Leishmania* strains can be exported through dogs. Specific species of *Leishmania* are no longer circumscribed to particular regions. In Europe, controlling this vector-borne disease seems essential because leishmaiasis is already endemic to southern Europe and new species may be introduced (*10*).

CL caused by *L. killicki* will probably soon become more common among persons who travel throughout North Africa. Because of the chronic evolution of CL lesions, clinicians should characterize the *Leishmania* strain and, if necessary, adapt their patient care to the strain.

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East African Trypanosomiasis in a Pregnant Traveler

To the Editor: Human African trypanosomiasis (HAT) results in a large number of deaths and considerable illness in sub-Saharan Africa. Although the disease is uncommon in returning travelers from that region, awareness of it is important for medical practitioners in areas where the disease is not endemic. The disease can be categorized geographically into West and East African trypanosomiasis caused by *T. brucei gambiense* and *Trypanosoma brucei rhodesiense*, respectively, and clinicopathologically into hemolymphatic (stage I) disease and meningoencephalitic (stage II) disease (*1*). The East African form of the disease is less common than the West African form and accounts for 10% of the global incidence of trypanosomiasis.

Relative stability in East African nations may have contributed to the lower incidence of the disease in these countries, but drought and increasing pressure on water sources may lead to an upsurge in East African disease. The increasing ease of global travel and attraction of game safaris and hunting may also lead to increasing exposure in travelers. HAT is treated with toxic drugs in regimens that have changed little for decades. Few published data exist on the treatment of HAT in pregnancy, particularly for East African disease. We describe a case of *T. brucei rhodesiense* infection occurring in a pregnant traveler.

A 32-year-old woman, 20 weeks pregnant, returned from a 9-day safari trip to Tanzania 8 days before coming to a hospital in London. She described a short history of fever, headache, and soft-tissue swelling of the forehead with severe regional adenopathy. She had evidence of skin necrosis (chancre) (Figure) but no history of tsetse fly bite. Blood tests showed anemia (hemoglobin 9.5 g/dL), leukopenia (1.8×10^9 cells/L), and thrombocytopenia (60×10^9 cells/L). A blood film showed trypomastigotes of *T. brucei rhodesiense*. Suramin was initially unavailable for treatment, but because of her deteriorating clinical state, she was treated with 1 dose of pentamidine (4 mg/kg) before suramin was obtained. Suramin was begun 36 hours after admission, initially at 5 mg/kg and increased over the next 2 doses up to 1 g. During the next 48 hours, her fever resolved, and serial blood films showed clearance of the parasites from the blood. A cerebrospinal fluid sample showed no signs of stage II disease, and the patient continued on suramin, completing a standard course as an outpatient. Her pregnancy was closely monitored, and she gave birth at term to a healthy baby girl.

The treatment of choice for stage I HAT caused by *T. brucei gambiense* is parenteral pentamidine (*1*). No published trials compare pentamidine and suramin in East African trypanosomiasis, but longstanding consensus suggests that suramin is more likely to be efficacious in stage I East African disease (*1*). The basis for this difference in efficacy is unexplained.

Theoretically, pentamidine may be teratogenic because it inhibits protein and nucleic acid synthesis in vitro (*2*). However, studies in rats found pentamidine to be feticidal but not teratogenic (*3*). Pentamidine has been used extensively for HAT prophylaxis without reported problems (*4*) and has had limited use in pregnant women with *Pneumocystis jirovecii* pneumonia. It continues to be recommended in pregnant women with stage I HAT originating in West Africa. Suramin is known to cause a syndrome similar to preeclampsia in pregnant rats (*5*), yet it too has been used in large-scale treatment programs for onchocerciasis, and no fetal or placental effects have been reported in humans (*2*,*6*). We found 1 case report describing successful use of suramin, followed by melarsoprol, in a pregnant woman with HAT (*7*).

The treatment of stage II disease in pregnancy is problematic, and published information to guide therapy is lacking. Although the effect of arsenicals on fetuses is a concern, case reports have described the successful use of melarsoprol during pregnancy (*7*,*8*); if left untreated, the disease is fatal. Thus, if our patient had stage II disease, use of melarsoprol, which is

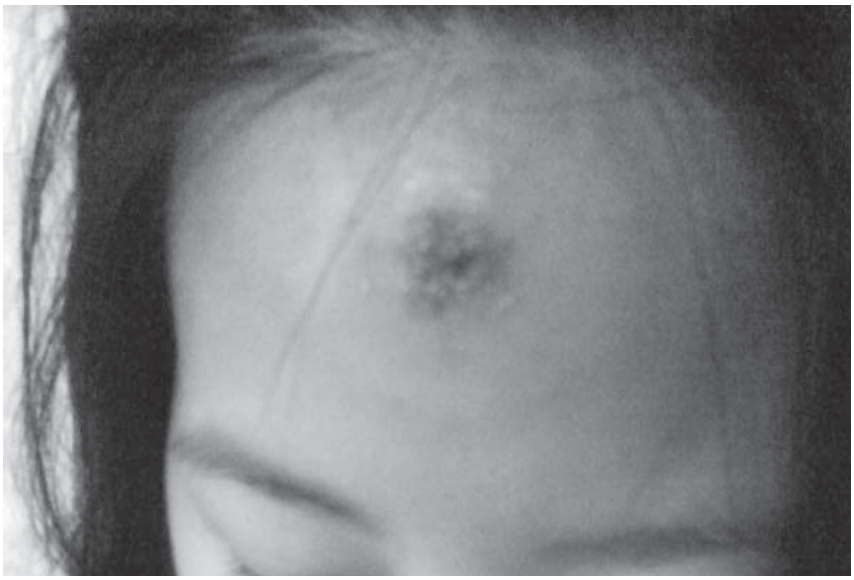

Figure. Chancre at site of tsetse fly bite on forehead of pregnant patient with trypanosomiasis. A color version of this figure is available online (www.cdc.gov/EID/content/15/11/1866-F.htm).

often given with prednisolone, would have been necessary.

In pregnant women with West African (*T. brucei gambiense*) stage II disease, either melarsoprol or eflornithine can be used, but neither is effective for East African disease. Although eflornithine can abort early pregnancies and cause disordered organogenesis (*9*), the severe encephalopathy associated with melarsoprol makes eflornithine a preferable option for single-agent treatment. However, nifurtimox–eflornithine combination therapy will soon replace single-drug regimens for stage II *T. brucei gambiense* cases (*10*).

We believed evidence was insufficient to withhold suramin therapy for this highly fatal disease. Because of the uncertainty about effects of pregnancy on the ability to clear trypanosomes, the patient will be followed up for signs of relapse. The danger of HAT should be specifically highlighted for all travelers to trypanasomiasis-endemic regions, particularly pregnant travelers because of potential harm to unborn children.

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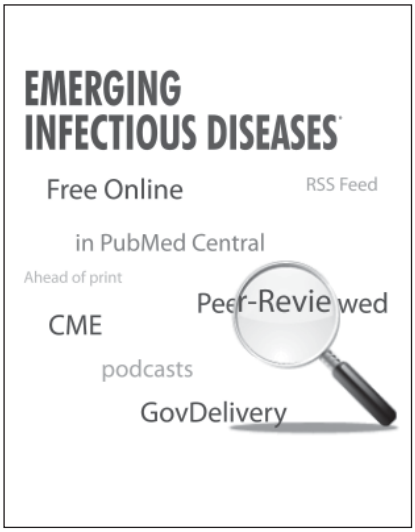

Rickettsia africae Infection in Man after Travel to Ethiopia

To the Editor: The first human case of African tick-bite fever was described in 1992 as occurring in Zimbabwe. The causative agent was identified as a new serotype of the spotted fever group (SFG) rickettsiae and named *Rickettsia africae* (*1*). These findings confirmed observations made by Pijper in the 1930s which suggested that there were 2 different kinds of human SFG rickettsioses in sub-Saharan Africa: Mediterranean spotted fever caused by *R. conorii* and transmitted by *Rhipicephalus* species, ticks of dogs, and African tick-bite fever caused by *R. africae* and transmitted by *Amblyomma* species, ticks of cattle and wild ungulates. African tick-bite fever has subsequently been diagnosed in patients from several other sub-Saharan countries and also from the West Indies (*2*,*3*).

In a recent analysis of the spectrum of diseases among returning travelers, tick-borne spotted fever was (after malaria) the second most frequent cause of systemic febrile illness among those returning from sub-Saharan Africa. It occurred more frequently than typhoid fever and dengue fever (*4*). The following case description reports an infection with *R. africae* in a man in France who recently returned from Ethiopia.

On November 4, 2005, a 62-year-old French man sought care at the Medical Center of the Institut Pasteur in Paris for fever, along with chills, headache, neck and shoulder pain, and fatigue over the previous 4 days. At the onset of these symptoms he had noticed dark nodular lesions on his neck and his left groin followed 2 days later by a slightly painful eruption on his arms and his trunk. He had spent a month in southwest Ethiopia, north of Kelem near the Sudanese bor-

der, and returned to France on October 26, 2005. While in Ethiopia, he had assisted with a production of a documentary film about an Ethiopian tribe and had been in contact with cattle in the villages. He had not noticed any tick bites. On physical examination he had a fever of 38°C, a nodular lesion with a central dark crust on his neck, a second lesion on his left inguinal fold (Figure, panel A), and a vesicular eruption on his arms and his trunk (Figure, panel B). Leukocyte count was 3,200, including 1,869 neutrophils and 867 lymphocytes. The platelet level was 174,000/mm^3. The C-reactive protein level was 28.3 mg/L. The aspartate aminotransferase level was slightly elevated. The patient was treated with doxycycline 200 mg/day for 1 week for suspected African tick-bite fever. Follow-up showed a quick recovery from his symptoms except for fatigue that persisted for ≈1 month.

A commercial immunofluorescence assay for *R. conorii* and *R. typhi* immunoglobulin G performed both on an initial blood sample and a second sample taken 1 week later were negative. A blood sample and a biopsy specimen of the inguinal eschar were sent to the National Reference Center of Rickettsiae in Marseille, France. Although cellular culture of both specimens and molecular testing of the blood sample were negative, PCR for the sequences of citrate synthase (GenBank accession no. RAU59733, 93.1% homology) and rickettsial OmpA (GenBank accession no. RAU83436, 99.3% homology) applied on the skin biopsy detected *R. africae* and confirmed the diagnosis of African tick-bite fever.

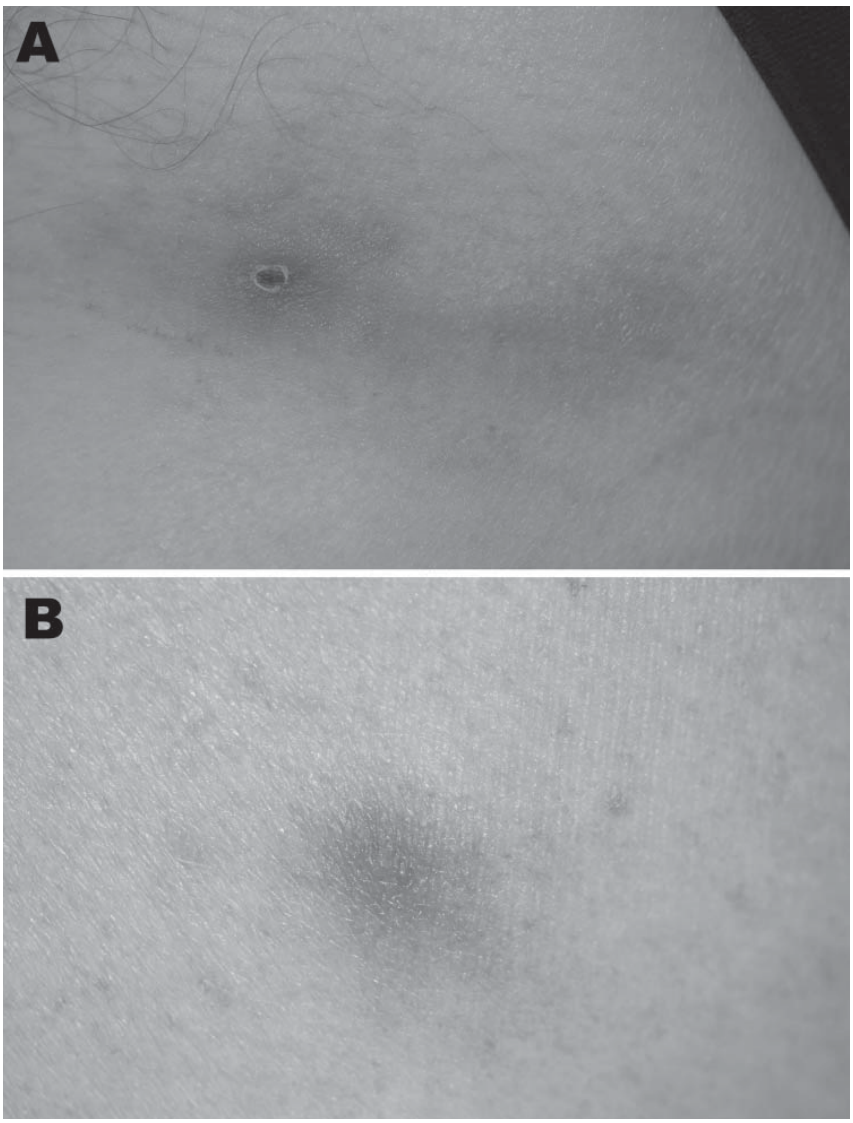

Figure. Inoculation eschar on left inguinal fold (A) and vesicular skin lesion (B) in a traveler recently returned to France from Ethiopia.

From 1969 to 1971, SFG rickettsiae were isolated from *Amblyomma* spp. ticks collected in Ethiopia. They were regarded as *R. conorii* or as closely related bacteria (*5*). Later, more specific tests using western immunoblots with monoclonal antibodies showed that these rickettsiae differed from *R. conorii* (*6*). In 1992 SFG rickettsiae isolated from *Amblyomma* ticks collected in Zimbabwe and from the blood of a patient in Zimbabwe were compared to *R. conorii*, to other pathogenic SFG rickettsiae, and to a SFG rickettsia isolated from an *Amblyomma* spp. tick in Ethiopia 20 years before. The SFG rickettsia isolates from Ethiopia were identical to isolates obtained in Zimbabwe from the *Amblyomma* ticks and the patient's blood and were different from *R. conorii* and other pathogenic SFG rickettsiae. This new serotype of SFG rickettsiae was named *R. africae* (*1*,*7*). A recent study confirmed the presence of *R. africae* in ticks collected in Ethiopia, as well as *R. aeschlimanii* (*8*). Thus, evidence of *R. africae* in Ethiopia has been known for a long time.

The geographic distribution of African tick-bite fever is related to the presence of *Amblyomma* spp. ticks, vectors and reservoirs of *R. africae*. Consequently African tick-bite fever should also be considered as a possible diagnosis in patients with febrile illness returning from countries where *R. africae* has been detected in *Amblyomma* ticks, even if a human infection has not yet been reported (*9*,*10*).

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Rickettsia massiliae in the Canary Islands

To the Editor: *Rickettsia massiliae* was recently recognized as a human tick-borne spotted fever group rickettsia (*1*). We report the finding of *R. massiliae* in *Rhipicephalus pusillus* ticks from Gran Canaria, Canary Islands, Spain. Introduction of this pathogen into the Canary Islands is thought to have resulted from translocation of the European wild rabbit *Oryctolagus cuniculus* (Linnaeus), a preferred host of *R. pusillus* ticks (www.kolonin.org/16_4.html), from the Iberian Peninsula 600 years ago (*2*).

We collected questing adult ticks in 2008 in Gran Canaria and identified 2 tick species, *Hyalomma lusitanicum* (n = 82 [46 females]) and *R. pusillus* (n = 8 [5 females]). Whole ticks were preserved in 70% ethanol and used for DNA extraction by using TriReagent (Sigma, St. Louis, MO, USA) according to the manufacturer's instructions. We identified rickettsial sequences by using PCR primers that amplify fragments of 16S rRNA, *ompB, atpA, dnaA, dnaK*, and *recA* genes (Table). Amplicons were cloned into pGEM-T (Promega, Madison, WI, USA), and 3 independent clones were sequenced from both ends for each gene marker. Sequence similarity search was performed by using BLAST (www.ncbi.nlm.nih.gov). Rickettsial DNA was detected in 2 *R. pusillus* males only; sequences were identical in both ticks. Fragments of 16S rRNA were 99% identical to the *R. massiliae* strain Mtu5 (CP000683) isolated from *R. sanguineus* ticks in southern France (*3*), and fragments of *ompB, atpA, dnaA, dnaK*, and *recA* genes were 100% identical to the *R. massiliae* strain Bar29 (AF123710, AY124739, DQ821798, DQ821828, and AY124750, respectively), previously isolated from *R. sanguineus* ticks in Catalonia, Spain (*4*) (Table).

R. massiliae was first isolated in 1992 from *R. sanguineus* ticks collected near Marseille, France (*5*). Since then, the pathogen has been identified in different *Rhipicephalus* species in France, Greece, Portugal, Switzerland, Spain, North and Central Africa, Argentina, and the United States (*6*,*7*). *R. massiliae* has been identified in southern Spain (*8*) but not in the Canary Islands. *R. pusillus* ticks are commonly found in southern Europe (Portugal, Spain, and France) and northern Africa (Tunisia and Morocco). All stages of these ticks inhabit burrows of wild rabbits and feed on them (www.kolonin.org/16_4.html).

Wild rabbits were introduced into the Canary Islands at the end of 14th century during colonization by the kingdom of Castilla. Colonists were asked to bring rabbit couples with them to provide food in the islands (*2*), a practice continued by new colonists because of their interest in hunting this rabbit species. Introduction of wild rabbits by colonists led to establishment of parasites, such as helminths, coccidia, and viruses in the Canary Islands (9). *R. pusillus*, a common ectoparasite (tick) that feeds on wild rabbits on the Iberian Peninsula, was also introduced this way. *R. massiliae* could have been introduced in the islands by infected *R. pusillus* ticks or by infected wild rabbits if this species serves as a natural reservoir host for the pathogen.

To find evidence for this hypothesis, we tested blood and liver samples of 150 wild rabbits from both Canary Islands and Andalucía (southern Spain) by using *Rickettsia*-specific PCR primers (Table). No *R. massiliae* DNA was detected in the rabbit samples tested,

Table. *Rickettsia massiliae* PCR conditions and amplicon size, Canary Islands, 2008*

Gene	Description (GenBank accession no.)	Primer sequence (5′ → 3′)	Amplicon size, bp	PCR annealing conditions
16S rRNA	16S ribosomal RNA (GQ144453)	F: AGAGTTTGATCCTGGCTCAG R: AACGTCATTATCTTCCTTGC	416	50°C/30 s
ompB	Outer membrane protein (GQ144450)	F: GGGTGCTGCTACACAGCAGAA R: CCGTCACCGATATTAATTGCC	618	53°C/30 s
dnaK	Heat-shock protein 70 (GQ144451)	F: AGCGTCAAGCAACGAAAGAT R: CAAACGTTGAAGTGCTAAAGG	323	50°C/30 s
dnaA	Chromosomal replication initiation protein (GQ144449)	F: CCTACTAACTTTGTTAGAGATT R: TGATGATTCTGCAACCGCTC	241	56°C/30 s
recA	RecA recombination protein (GQ144452)	F: TGCTTTTATTGATGCCGAGC R: CTTTAATGGAGCCGATTCTTC	428	52°C/30 s
atpA	ATP synthase F1 alpha subunit (GQ144448)	F: ACATATCGAGATGAAGGCTCC R: CCGAAATACCGACATTAACG	731	48°C/30 s

*GenBank accession numbers correspond to *R. massiliae* sequences identified in this study. PCRs were completed by employing the Access RT-PCR system (Promega, Madison, WI, USA) with 1 ng DNA, the oligonucleotide primers, and annealing conditions and with extension for 1 min at 68ºC. F, forward; R, reverse.

suggesting that the pathogen probably was introduced in the Canary Islands with infected *R. pusillus* ticks feeding on rabbits. Alternatively, *R. massiliae* infection levels in wild rabbits may be below the PCR detection limit and were not detected.

The Canary Islands are a popular tourist destination. The presence of *R. massiliae* in the islands constitutes a risk for human infection and should be considered in hospital diagnostic and wildlife management strategies. As with other *Rhipicephalus* spp., *R. pusillus* ticks could feed on humans under certain circumstances (*10*). Our results emphasize the risks associated with unsupervised animal translocations, a factor that probably plays a role in the introduction of ticks and tick-borne pathogens in different parts of the world.

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Dengue Virus Type 3 Infection in Traveler Returning from West Africa

To the Editor: GeoSentinel, the global surveillance program of the International Society of Travel Medicine, recently reported that returning travelers may serve as sentinels for local outbreaks of dengue fever in tropical areas to which it is endemic (*1*). We investigated a case of dengue virus (DENV) type 3 (DENV-3) infection in a traveler returning to France from West Africa, which provided evidence for DENV-3 circulation in Côte d'Ivoire.

A 53-year-old French expatriate living in Abidjan, the economic capital of Côte d'Ivoire, arrived in France on July 17, 2008, and was hospitalized 4 days later with fever of 40°C, headache, asthenia, anorexia, chills, diffuse arthralgia, and myalgia. Results of a physical examination were normal except for a diffuse nonpetechial macular rash and moderate hepatosplenomegaly. A tourniquet test was not performed. At admission, platelet count was 103 cells/mm^3 and leukocyte count was 2,410 cells/mm^3. Thin and thick blood smears and results of the immunochromatographic test (Binax NOW malaria tests; Binax, Portland, ME, USA) were negative. The patient recovered without sequelae and was discharged 6 days after admission.

At admission, chikungunya virus–specific immunoglobulin (Ig) G and IgM were not detected by indirect immunofluorescence tests (*2*). IgG, but not IgM, specific for DENV was detected by an immunochromatic test (Panbio Dengue Duo Cassette; Biotrin, Lyon, France) and confirmed by ELISA (PanBio dengue duo test). However, DENV RNA was demonstrated in serum by using 4 reverse-transcription–PCR (RT-PCR)–based assays: a positive result in a flavivirus universal assay (*3*), a positive result in a DENV-1–4 real-time RT-PCR (*4*), a positive result in a DENV-3–specific RT-PCR, and a negative result in a specific RT-PCR for DENV-1, -2, and -4 (*4*). The concomitant finding of DENV RNA and IgG against DENV suggests the patient had dengue infection before this episode.

DENV-3 viremia was confirmed by sequencing a 547-nt region of the envelope gene (GenBank accession no. FJ587232, nt 852–1398 referring to the H87 DENV-3 prototype strain). Our sequence aligned with homologous DENV-3 sequences retrieved from GenBank and used for phylogenetic analysis (Figure). Our patient, in whom classic dengue fever was diagnosed, was infected with a strain that belonged to genotype III most closely related to strains isolated in Singapore, Taiwan, Sri Lanka, India, and Saudi Arabia. Its closest relatives were the strain from Saudi Arabia isolated in 2004 and another strain claimed in ProMED by Japanese researchers to have been isolated in 2008 from a Japanese traveler returning from Côte d'Ivoire (*6*). Therefore, this strain is likely to have originated in the Middle East, the Indian subcontinent, or Southeast Asia rather than in Central or South America.

In Africa, most data on epidemic or endemic dengue activity originate in East Africa. Dengue fever was seldom reported in West Africa. In 2000, DENV-1 was isolated from a French soldier in Côte d'Ivoire (*7*). More recently, an outbreak caused by DENV-2 occurred in Gabon in West Africa (*8*). In this context, it is notable that

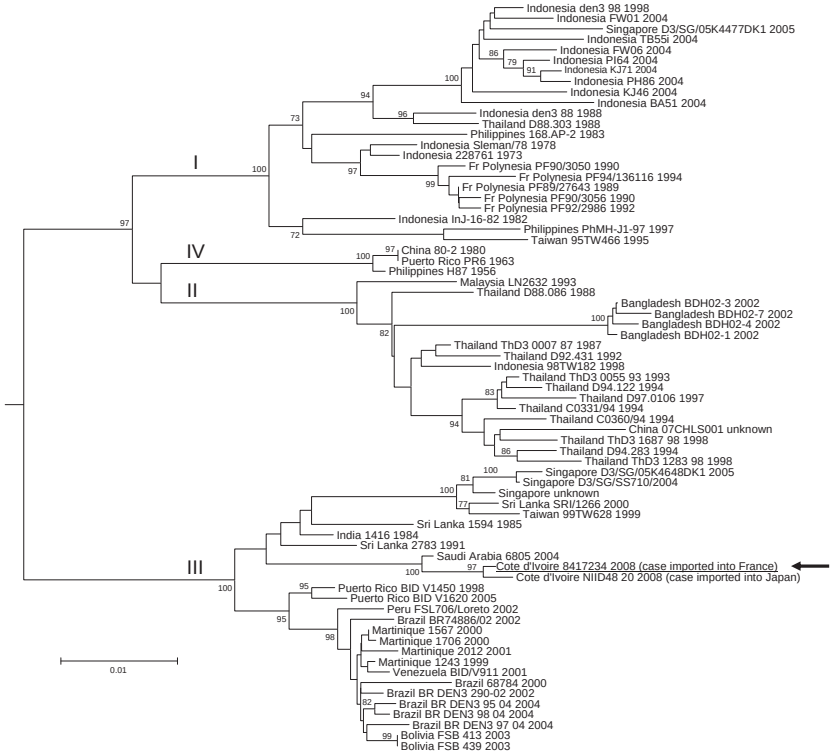

Figure. Phylogenetic analysis of selected dengue virus type 3 (DENV-3) sequences. The main genotypes are indicated using roman numerals at the node of the lineage. Sequence identification is as follows: country of origin, strain name, year of isolation/detection. The sequence determined in our study is underlined and designated by an arrow. Phylogenetic studies were conducted by using MEGA version 2.1 (*5*). Genetic distances were calculated with the Kimura 2-parameter method at the nucleotide level. Phylogenetic trees were constructed using the neighbor-joining method. The robustness of the nodes was tested by 500 bootstrap replications. The tree was rooted with DENV-1, DENV-2, and DENV-4 sequences. Scale bar indicates nucleotide substitutions per site.

DENV-3 strains recently caused unexpected outbreaks of dengue hemorrhagic fever in Sri Lanka, East Africa, and Latin America (*9*).

The case presented here demonstrates that epidemics may be undetected or unidentified until diagnosis is assessed in another country from a returning infected visitor, thus drawing attention to an unidentified potential epidemic situation. This situation can be unraveled by a clinician who considers geographic factors in the diagnostic workup and has access to and uses appropriate laboratory capacity to diagnose imported infections. At the time dengue was diagnosed in this patient, cases of yellow fever were reported in the same location of Côte d'Ivoire (Abidjan) (*5*), illustrating concomitant circulation of 2 viruses in which dengue may have remained undetected in the absence of a laboratory-confirmed case in the traveler's home country. Therefore, this case reinforces the utility of travelers as sentinels for infectious diseases as previously reported (*10*). Our findings reiterate the need for technologic transfer of PCR-based direct diagnostics to reference centers in areas where emergence is likely. These efforts also should embrace serology and encourage close collaboration with world reference centers for confirmation and characterization (*10*).

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Low Immunity to Measles and Rubella among Female Guest Workers, Northern Mariana Islands

To the Editor: The Commonwealth of the Northern Mariana Islands (CNMI), a group of northern Pacific islands in political union with the United States, was exempt from US labor laws until 2007. This exemption attracted business opportunities, which led to a high demand for guest workers. The Centers for Disease Control and Prevention advises the US Citizenship and Immigration Services of vaccination requirements for those applying for immigration and work visas before the applications are approved (*1*). Since 1996, all applicants born after 1957 and >12 months of age have been required to provide evidence of completed vaccination against, or of immunity to, measles, mumps, and rubella viruses. Those unable to provide such evidence must receive at least 1 dose of the vaccines recommended by the US Advisory Committee on Immunization Practices before visa approval. The Committee also advises applicants to receive additional doses of the required vaccines after arrival in the Mariana Islands. We aimed to determine the proportion of CNMI guest workers who were immune to measles and rubella by testing a convenience sample of serum collected during September and October 2006. However, procedures for validating the vaccination status for our sample population are unknown. Given our results, it appears that validation procedures of immunity status in guest workers or immigrants to the United States were suboptimal at the time of this study.

Serum samples from 210 female workers from 17 through 51 years of age were collected opportunistically when, as a requirement for annual con-

tract renewal, the workers came to the Department of Public Health, Saipan, CNMI. Approximately 70% of these guest workers were from the People's Republic of China and the Philippines and were employed in the garment and hospitality industries (*2*). We estimated that a minimum sample size of 196 would provide a precision estimate of 5% based on an anticipated proportion immune of 85% (actual study size was 210 samples). Informed consent was obtained from all participants. Serum samples, with identifying information removed, were shipped to the Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia.

Immunoglobulin G against measles and rubella was detected in serum by using Enzygnost ELISAs (Dade Behring, Deerfield, IL, USA) according to manufacturer's instructions. For measles and rubella, samples with optical density (OD) values >0.2 (equivalent to 330 mIU/mL) indicated protective immunity and samples with OD values <0.1 were suggestive of no protection (*3*). Samples with OD values in the equivocal range (0.1–0.2) were retested, and the repeat result was recorded. Repeat equivocal results were classified as not protected. Data were analyzed by using STATA version 8.2 (Stata Corp., College Station, TX, USA). Exact binomial 95% confidence intervals were calculated. Proportions of guest workers immune to measles and rubella, by age group and country of origin, were assessed by Fisher exact test and χ^2 statistics.

The proportion of Chinese guest workers immune to measles (115/154, 74.7%) and rubella (131/154, 85.1%) was lower than the proportion immune of all other workers combined (56/56, 100% and 50/56, 89.3%, respectively), but the difference was only significant for measles (Table). When compared with Chinese workers of all other ages, Chinese workers 20–34 years of age were significantly less likely to be protected against measles (69.3% vs. 89.7%; p = 0.01). No significant differences were found in the proportion of guest workers immune to rubella by age group (p = 0.70) or country of origin (p = 0.43).

A limitation of our work is that the sample may not be representative of the CNMI guest worker population overall. Only 27% of guest workers in the CNMI are from China, and 43% are from the Philippines (J.-P. Chaine, pers. comm., March 2008), whereas in our study 73% of guest workers were from China, and 23% were from the Philippines. Also, no men were recruited for the study yet men represent 19% of guest workers from China (J.-P. Chaine, pers. comm., March 2008), so our findings should not be extrapolated to this group.

China and the Philippines report 94% and 92% childhood immunization coverage with 1 measles vaccine, respectively (*4*,*5*). Similar to other reports of low measles immunity in young adult populations (*6*), this study identified young adult female workers from China as a group particularly susceptible to measles infection with >25% (39/154) unprotected. Neither country implemented rubella vaccination before 2006, and the immune profile for rubella reflects age-specific seroprevalence for endemic disease; >10% of these women remain susceptible to rubella during their potential childbearing years (*7*).

More than 8,000 female workers from China were in the CNMI during the period of this survey, and as many as 2,000 may have been susceptible to measles, which would have facilitated sustained transmission if the virus had been introduced. Several studies have shown that unvaccinated persons are clustered geographically or socially and may be at increased risk for measles or rubella outbreaks (*8*,*9*). These reports underscore the possible risk of virus spread in populations with low immunity in Saipan.

Table. Proportion of guest workers immune to measles and rubella by ethnicity and age group, Northern Mariana Islands, September–October 2006*

	Proportion immune					
	Guest workers from China			Guest workers from other countries†		
Age group, y	Total no. tested	No. (%) measles, 95% CI	No. (%) rubella, 95% CI	Total no. tested	No. (%) measles, 95% CI	No. (%) rubella, 95% CI
15–19	18	17 (94.4), 72.7–99.9	14 (77.8), 52.4–93.6	0	–	–
20–24	56	41 (73.2),59.7–84.2‡	49 (87.5), 75.9–94.8	1	1 (100), 2.5–100§	1 (100), 2.5–100§
25–29	40	25 (62.5), 45.8–77.3‡	36 (90.0), 76.3–97.2	10	10 (100), 69.2–100§	10 (100), 69.2–100§
30–34	18	13 (72.2), 46.5–90.3‡	15 (83.3), 58.6–96.4	9	9 (100), 66.4–100§	8 (88.9), 51.8–99.7
35–39	17	14 (82.4), 56.6–96.2	13 (76.5), 50.1–93.2	16	16 (100), 79.4–100§	15 (93.8), 69.8–99.8
40–44	2	2 (100), 15.8–100§	2 (100), 15.8–100§	14	14 (100), 76.8–100§	11 (78.6), 49.2–95.3
>45	2	2 (100), 15.8–100§	1 (50.0), 1.3– 98.7	6	6 (100), 54.1–100§	5 (83.3), 35.9–99.6
Total	153¶	114 (74.5), 66.8–81.2#	130 (85.1), 78.3–90.2	56	56 (100), 93.6–100§	50 (89.3), 78.1–96.0

*CI, confidence interval.
†Philippines (n = 48), Japan (n = 6), South Korea (n = 1), Thailand (n = 1).
‡Significant difference in measles immunity of Chinese workers 20–34 years of age compared with that of Chinese workers of other age groups; p = 0.01.
§1-sided confidence interval.
¶The age of 1 guest worker was not provided by the referring laboratory.
#Significant difference in measles immunity between workers from China and other countries; p<0.001.

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Pneumonia Caused by *Shigella sonnei* in Man Returned from India

To the Editor: Shigellosis is a cause of infectious dysentery frequently occurring in developing countries yet usually associated with diarrhea in travelers from regions where *Shigella* infections are endemic. *Shigella* spp. are usually spread directly from person to person by the fecal–oral route or indirectly by fecal contamination of food or water with ingestion of feces contaminated food or water (*1*). Aside from clinical intestinal manifestations, shigellosis causes a wide variety of extraintestinal signs, such as bacteremia or neurologic manifestations (*2*).

Pneumonia is an atypical but potential complication of shigellosis. In developing countries, *Shigella sonnei* and *S. flexneri* infections were reported to cause acute pneumonia in malnourished infants and, in these cases, were associated with severe prognosis and a death rate of 14% (*3*).

We describe a case of severe pneumonia caused by *S. sonnei* that developed in a man from Italy who had traveled to India. This is an atypical case of shigellosis occurring in an immunocompetent person, generally healthy and without any underlying severe predisposing condition.

A 69-year-old white man was admitted to the emergency unit of the Presidio Ospedaliero, Department of Infectious Diseases, Treviso, Italy, on February 24, 2008, with severe dyspnea and a cough producing purulent sputum. He had traveled to India and had visited urban and rural areas over a 15-day period. He returned home 7 days before hospital admission. During his travel, the patient reported episodes of vomiting and moderate diarrhea without fever. These signs were resolved 4 days before his return to Italy. Initial examination showed he had a temperature of 37°C and an oxygen saturation of 88% in room air. Arterial blood gas levels were pH 7.42, partial pressure of oxygen in arterial blood 42 mm Hg, and partial pressure of carbon dioxide 35 mm Hg. Because of his progressive respiratory failure, he was transferred to the intensive care unit. Relevant laboratory tests were performed, and abnormal values of erythrocyte sedimentation rate 85 mm/h, C-reactive protein 105 mg/L, hemoglobin 10.2 g/dL, and neutrophilia were found.

A chest radiograph showed diffuse pneumonia with infiltrates. A computed tomography scan of the thorax showed nodular lesions and cavity formations. No neurologic or abdominal abnormalities were found, and peristalsis was within normal limits.

Sputum and bronchial alveolar lavage (BAL) smears showed gram-negative microorganisms. Melioidosis was suspected because the man had traveled to a known melioidosis-endemic area. In view of this information, blood, sputum, and BAL samples were collected, and the patient was immediately given empirical antimicrobial drug therapy with amoxicillin/clavulanic acid, plus meropenem and norfloxacin. Given the absence of gastrointestinal symptoms and because shigellosis was not suspected, stool samples were not obtained. Specimens were sent to the Istituto Superiore di Sanità, Infectious Diseases Department for bacteriologic examination. Blood cultures were negative; gram-negative rods were recovered from the sputum and BAL smears. The microorganisms were identified as *S. sonnei*

by the API 20E strip (bioMerieux Italia, Florence, Italy). The bacteria agglutinated in *Shigella* group D antiserum but failed to agglutinate in *Shigella* groups A, B, and C antisera (Becton Dickinson Diagnostic Systems Italia, Milan, Italy). To further confirm bacterial identification, we amplified the full length of 16S rRNA nucleotide sequence by using the universal primers for eubacteria, 16S rRNAs (27f 5′-GAGAGTTTGATCCTGGCTCAG-3′ and 1495r 5′-CTACGGCTACCTTG TTACGA-3′) and sequenced the PCR product. The sequence obtained was compared by using the BLAST search tool (www.ncbi.n/m.nib.gov/BLAST), which showed 100% identity with the 16S rRNA *S. sonnei* strain AU65 sequence GenBank accession no. EF032687). Antimicrobial drug susceptibility of the isolate was determined for 26 agents by the disk-diffusion method in Mueller Hinton agar, according to the Clinical and Laboratory Standards Institute. The isolate was susceptible to amikacin 30 μg/mL, ceftazidime 30 μg/mL, ceftriaxone 30 μg/mL, meropenem 10 μg/mL, sulfisoxazole 0.25 μg/mL, sulfonamides 300 μg/mL, and triple sulfa 23.75/1.25 μg/mL; intermediate to cefotaxime 30 μg/mL, gentamicin 10 μg/mL, kanamycin 30 μg/mL, and tobramycin 10 μg/mL; and resistant to amoxicillin 25 μg/mL, amoxicillin/clavulanic acid 20/10 μg/mL, ampicillin 10 μg/mL, ampicillin-sulbactam 20 μg/mL, cefoxitin 30 μg/mL, chloramphenicol 30 μg/mL, ciprofloxacin 5 μg/mL, clarithromycin 15 μg/mL erythromycin 15 μg/mL, nalidixic acid 30 μg/mL, norfloxacin 10 μg/mL, streptomycin 10 μg/mL, tetracycline 30 μg/mL, and trimethoprim 5 μg/mL.

The patient was discharged from hospital after 40 days. At follow-up 6 months later, his general health status was good, and a chest radiograph showed no abnormalities.

Extraintestinal signs associated with *S. sonnei* infections are generally reported as secondary manifestations of dysentery. In particular, bacteremia is reported as a gastrointestinal complication in infants in developing countries (*4*) or in immunocompromised adults (*5*); pneumonia associated with *S. sonnei* is more rare but possible and has been described in malnourished children (*4*,*6*), in human immunodeficiency virus–infected patients (*7*), and in patients with chronic diseases (*8*–*10*). Generally, in these cases, pneumonia is associated with bacteremia.

This reported case of severe pneumonia related to *S. sonnei* is unusual in a healthy patient with self-limiting dysentery whose symptoms and clinical conditions were not suggestive of bacteremia. Vomiting and aspiration of mixed mouth flora containing *Shigella* spp. could be a possible cause of pneumonia in this patient. However, the hematogenous route cannot be excluded. A potential explanation of the severe illness could be that in healthy elderly people the immune system functions are less vigorous and thus more susceptible to infections. Nevertheless, the acute episode in this patient was effectively treated by a combination of meropenem, norfloxacin, and amoxicillin/clavulanic acid, although the bacterium is resistant to the latter 2 drugs.

This case report should be of particular interest for clinicians because it describes an atypical case of extraintestinal shigellosis and an example of misdiagnosis of melioidosis. Clinicians should be alert for pneumonia associated to *Shigella* spp. or *Burkholderia pseudomallei,* specifically in healthy people who have traveled to areas to which these pathogens are endemic.

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Imported Human Fascioliasis, United Kingdom

To the Editor: We initiated enhanced surveillance for human fascioliasis after a reported increase in livestock cases in the United Kingdom. From January 1, 2008, through January 31, 2009, 11 human cases were confirmed by the reference laboratory for England and Wales, compared with 6 cases during the preceding 10 years. The Scottish reference laboratory detected no human cases during the study period.

Fascioliasis was defined as a positive *Fasciola* immunofluorescent antibody test with a screening titer of 1:32 and either compatible clinical or radiologic features consistent with the disease. We obtained clinical and radiologic information from the referring physician. Clinical features of both acute and chronic infection include fever, upper abdominal pain, malaise, eosinophilia, and impaired liver function; therefore, distinguishing between the 2 phases can be difficult. Fifty percent of chronic infection is subclinical (*1*,*2*). Compatible radiologic features are capsular enhancement with contrast, hypodense nodular areas, and low-density serpiginous lesions (*2*). Our analysis comprised 11 cases (Table). Two patients were white British, both of whom had recently traveled to sub-Saharan Africa. Cases from the preceding 10 years diagnosed in our laboratory were all in persons with histories of travel to fascioliasis-endemic areas. Therefore, these cases do not provide firm evidence of indigenous zoonotic transmission within England and Wales.

Table. Characteristics of human fascioliasis case-patients during enhanced surveillance, United Kingdom, January 1, 2008–January 31, 2009*

Case no.	Age, y/sex	Country of origin	Years since migration	Other travel	Risk factor	Clinical features	Eosinophil count, x10^9/L)	Abnormal liver function	Hepatic imaging	IFAT†
1	45/F	Yemen	7	Yemen regularly	*Khat* use	Abdominal pain	8.4	Yes	Mixed-density liver lesion (CT)	1:128
2	44/M	Somalia	16	Ethiopia 2007	*Khat* use	Fever, abdominal pain	3.4	Yes	Serpiginous lesion (MRI)	1:64
3	34/F	Ethiopia	3	S. Africa regularly	*Khat* use	Fever, abdominal pain	11.4	No	Heterogeneous lesion (USS)	1:128
4	44/F	Somalia	7	Somalia 2004, Netherlands	*Khat* use	Abdominal pain	8.3	No	Heterogeneous lesion (USS)	1:128
5	54/F	Somalia	21 (to Netherlands), 4 (to UK)	None	*Khat* use	Anorexia	8.4	No	Low-density lesion (CT)	1:32
6	43/M	Somalia	28 (to India), 21 (to UK)	None	*Khat* use	Fever	1.0	Yes	Heterogeneous lesion (USS)	1:128
7	28/F	UK	–	Uganda 2007–2008	–	Abdominal pain, hepatomegaly	1.84	Yes	Hepatomegaly with large mixed cystic and solid lesion (USS)	1:512
8	67/M	UK	–	Kenya 2008, prior world travel	–	Malaise, abdominal pain	0.04	Yes	Multiple gallstones (MRCP)	1:256
9	38/M	Ethiopia	10	Ethiopia 2006	–	Abdominal pain, fever	18.7	Yes	Normal (USS, MRCP)	1:128
10	28/M	Ethiopia	Unknown	Unknown	–	Fever, gram-negative sepsis; new HIV diagnosis	<0.04	Yes	Lesion in hepatic vein	1:64
11	47/F	Somalia	16 (to Yemen), 6 (to UK)	Unknown	*Khat* use	Abdominal pain, fever	16.8	Yes	Low-density lesion (CT)	1:256

*IFAT, immunofluorescent antibody test; CT, computed tomography; MRI, magnetic resonance imaging; USS, ultrasound scan, MRCP, magnetic resonance cholangiopancreatography.
†Titer of IFAT (screening titer 32).

Nine patients originated from Somalia, Ethiopia, or Yemen. Few cases have previously been reported from this area (*3*), although Ethiopian migrants have been shown to have an egg positivity of 0.4% on routine screening (*4*). Patients 5 and 6 had not returned to Africa for >20 years, suggesting that they acquired their infection in Europe. Therefore, a risk factor may exist that is specific to this ethnic group within the United Kingdom.

Six cases were diagnosed at 1 hospital. All 6 patients reported current or past use of locally bought *khat*, a leaf chewed for its stimulant properties. It is imported fresh to the United Kingdom from Africa and is an ideal environment for the survival of *Fasciola* cercariae. It is used most commonly by migrants from the Horn of Africa and Yemen and has been reported in association with acute fascioliasis in the United Kingdom (*5*). Use of imported khat may explain the apparently higher incidence of fascioliasis in this ethnic group residing in the United Kingdom.

Despite the described parallel rise in human and veterinary fascioliasis, none of these cases provide clear evidence that recent human cases resulted from zoonotic transmission within the United Kingdom. Most cases occurred in migrants from the Horn of Africa and Yemen, some of whom may have acquired *Fasciola* spp. in their country of origin; other cases appear likely to have been acquired in the United Kingdom, possibly due to use of imported *khat*. Physicians need a heightened awareness of fascioliasis when investigating impaired liver function or abnormal abdominal imaging in migrants or travelers from high-risk areas.

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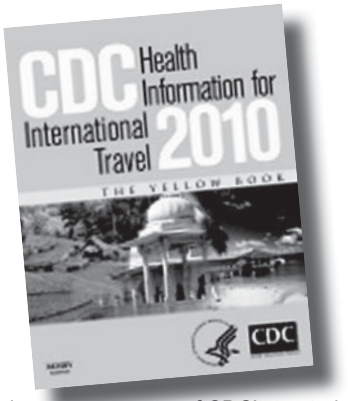

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Gastroenteritis Outbreaks in 2 Tourist Resorts, Dominican Republic

To the Editor: Noroviruses are an important cause of acute gastroenteritis, and outbreaks caused by these viruses have emerged as a major challenge to the healthcare, leisure, and tourism industries. The primary reason is their highly efficient transmission among persons in semiclosed populations such as those in healthcare facilities, hotels, and cruise ships. During an outbreak, primary cases result from exposure to a fecally contaminated vehicle (e.g., food or water), whereas secondary and tertiary cases among contacts of primary case-patients result from person-to-person transmission (*1*). Airborne and fomite transmission also play a role in the virus spread during outbreaks (*2*). Transmission through recreational water has also been described (*3*).

We investigated 2 outbreaks of norovirus gastroenteritis in tourist resorts in the Dominican Republic in January 2005. A total of 402 persons and 371 persons at 2 resorts, 1 located in Punta Cana (attack rate 6.8%) and another in Puerto Plata (attack rate 6.2%), respectively, reported symptoms of diarrhea, vomiting, headache, and fatigue. A total of 35 stools samples, 28 from Punta Cana and 7 from Puerto Plata, were negative for bacterial or parasitic pathogens. However, norovirus was confirmed by the IDEIA norovirus immunoassay (DakoCytomation, Ely, UK) in 11 samples from Punta Cana and 7 samples from Puerto Plata.

Active measures to reduce norovirus transmission were adopted by the 2 resorts, including an increase in cleaning frequency and increase in concentration of chlorine used for surface disinfection of public areas (1,000 mg/L), kitchenware (200 mg/L for 15 min), and fruits and vegetables (150 mg/L for 15 min). Personnel involved

in food preparation were invited to fill out an epidemiologic questionnaire and provide stool samples.

Because these preventive measures were not effective, water was suspected as a possible route of transmission, and diverse approaches were used to isolate viral RNA from different types of water. For sewage water, 100 mL were concentrated by a Molecular Weight Cutoff (MWCO) 100,000 Da Vivaspin20 centrifugal concentrator (Sartorius, Madrid, Spain) to a 5-mL concentrated sample. Five milliliters of chloroform:isoamyl alcohol (24:1) was added to the sample, mixed in a vortex, and centrifuged at 1,000 × *g* for 10 min (*4*). A second concentration step to 1 mL was performed with the resulting aqueous phase using a MWCO 100,000 Da Vivaspin6 centrifugal concentrator (Sartorius). For tap and recreational water, a sample of 2 L was processed through a cellulose nitrate filter, as described (*5*). The filter was first activated by 5 mL of 0.25 mol/L $AlCl_3$. After a washing step with 200 mL 0.5 mmol/L H_2SO_4, viruses were eluted from the filter with 10 mL of 1 mmol/L NaOH and neutralized with 50 µL of 0.1 mol/L H_2SO_4 and 1.1 mL 10× pH 8.0 Tris-EDTA buffer. Finally, samples were concentrated to a final volume of 1 mL with a Vivaspin6, centrifugal concentrator, as described above.

Viral RNA was isolated by the QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany), treated with Dnase I (Invitrogen, Carlsbad, CA, USA), and reverse transcribed to cDNA with Superscript II reverse transcriptase (Invitrogen). Finally, cDNA was amplified by multiplex-PCR with Taq Gold polymerase (Applied Biosystems, Foster City, CA, USA) by using forward primers Nor31N (5′-CAGATTAYACWGCWTGGGA-3′) and Nor32M (5′-CAGATTAYTCW CGWTGGGA-3′); and reverse primers Nor41M (5′-CCARTGATTTATGCTG TTCAC-3′) and Nor42N (5′-CCAGT GGGCGATGGAGTTC-3′), specific for the RNA polymerase gene (provided by J.A. Boga and M. Oña) (*6*). PCR was performed with the following conditions: 12 min at 94°C, (1 min at 94°C, 1 min at 55°C, 1 min at 72°C) for 40 cycles, and 10 min at 72°C. PCR products were analyzed by agarose gel electrophoresis. A band of 221 bp was considered a positive result for norovirus.

Norovirus was detected in the 4 samples of sewage water analyzed (2 from each location) collected after intervention, indicating that viral carriers still remained in the resorts. Moreover, norovirus particles were detected in the 2 depurated water samples (1 from each area), then indicating insufficient treatment conditions. Further investigation showed that depurated water was being used to water plants and grass by sprinkling, and becoming an important secondary source for infection. Norovirus-contaminated sewage was treated with different concentrations of chlorine and reverse transcription–PCR demonstrated that 15 mg/L for 1 h did not give a positive signal. Garden sprinkling watering was replaced by inundation watering. Although the virus was not detected either in tap or recreational water, hyperchlorination was carried out to prevent possible dissemination of norovirus. Preventive measures described above for surfaces, kitchenware and food were maintained for 2 additional weeks, and no additional cases were detected after 1 month had passed since the first case. To summarize, only interventions at multiple points, including eradication of secondary sources, and preventive measures to avoid person-to-person transmission enabled the outbreaks to be controlled.

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Hybrid El Tor *Vibrio cholerae* O1, Kuwait

To the Editor: The traditional causative agent of cholera, *Vibrio cholerae* O1, has 2 biotypes, classical and El Tor. The current seventh pandemic that began in 1961 and has spread to much of the world is caused by the El Tor biotype. This biotype has replaced the classical biotype responsible for the previous pandemics. The classical and El Tor biotypes are differentiated by phenotypic tests (*1*), and several nucleotide base differences occur at positions 115 and 203 in the *ctxB* gene (C in both positions in the classical and T in both positions in the El Tor biotype). These differences translate to histidine at amino acid position 39 and threonine at amino acid position 68 for the B subunit of cholera toxin (CT) in the classical biotype and tyrosine and isoleucine, respectively, for the corresponding amino acids in the El Tor biotype (*2*).

Recently, 3 variants of the El Tor biotype have been found. These are the Matlab variants, which could not be biotyped because they have a mixture of classical and El Tor traits (*1*); the Mozambique variant, which has a typical El Tor genome but a tandem repeat of the classical CTX prophage located in the small chromosome (*3*); and the hybrid El Tor variant, which has a typical El Tor biotype and an El Tor CTX prophage but produces CT of the classical type (*4*).

This hybrid El Tor variant has replaced the El Tor biotype in Dhaka and other parts of Bangladesh (*4*) and in India (*5*), Japan, Hong Kong, Zambia, the People's Republic of China, Sri Lanka, and Vietnam (*6*). Kuwait was affected by cholera in the mid 1960s during the current seventh pandemic. Subsequently, cholera disappeared from Kuwait as living standards improved. Screening of ≈5,000 acute-phase diarrheal stool samples in the mid-1980s in a major hospital in Kuwait did not yield *V. cholerae* O1 (*7*). The occasional cholera cases detected in Kuwait are imported, mainly from Asia through expatriate workers.

Two adult men, one who had just arrived from India and one who had just arrived from the Philippines, were admitted with severe watery diarrhea, vomiting, and dehydration to the Al-Adan Hospital, Kuwait, in November and December 2008, respectively. The patient from India reported eating in restaurants, and the patient from the Philippines had consumed fish soup just before the journey. Both patients were initially rehydrated with intravenous fluids.

Stool cultures were performed by using a battery of media, including thiosulfate citrate bile salt sucrose (TCBS) agar. Yellow colonies from TCBS agar were tested by using MicroScan WalkAway 96 (Dade Behring, West Sacramento, CA, USA) panel NBPC 34 and API 20E strip (bioMérieux, Marcy l'Etoile, France), which suggested *V. cholerae*. In slide agglutination tests, the colonies agglutinated with *V. cholerae* O1 polyvalent antiserum and Ogawa serotype antiserum (Denka-Seiken, Tokyo, Japan). The isolate from the patient from India was susceptible to tetracycline and ampicillin and resistant to co-trimoxazole, but the isolate from the patient from the Philippines was susceptible to all 3 of these antimicrobial agents in MicroScan (Dade Behring) and disk diffusion tests. Both patients were successfully treated with rehydration therapy and intravenous vibramycin (a semisynthetic tetracycline). Both *V. cholerae* O1 Ogawa isolates showed positive results in Vogues-Proskauer, chicken cell agglutination, and tube hemolysin tests and were resistant to polymyxin B (50 international units), results that suggest the El Tor biotype (*1*).

Both isolates were positive for the *ctxA* gene and El Tor–specific *tcp* gene but negative for classical-specific *tcp* gene by PCR (*8*). The genotype of the *ctxB* gene was determined by a mismatch amplification mutation assay PCR that detects polymorphism at nucleotide position 203; both isolates yielded a 186-bp amplicon with the classical biotype-specific primers and no amplicon with the El Tor biotype-specific primers (*9*).

The classical *ctxB* genotype of the isolates was further confirmed by sequencing the *ctxB* gene by using the BigDye termination method (Applied Biosystems, Foster City, CA, USA) with specific primers (*10*). This sequencing showed that both isolates had histidine at position 39 and threonine at position 68 in CT-B subunit. Thus, the isolates are hybrid variants that are phenotypically El Tor but genotypically classical for the *ctxB* gene.

Our findings suggest that cholera caused by the hybrid variant is present in the Philippines. The 2 cholera cases reported here were imported into Kuwait by travelers from cholera-endemic regions and were not endemic illnesses. The hybrid variant could possibly initiate the next cholera pandemic. Also, because CT is related to the major clinical sign of the disease, genetic changes in the molecule could result in alteration in the manifestation of the disease. The changes could also influence the effectiveness of cholera vaccines that contain CT-B as a component (*6*).

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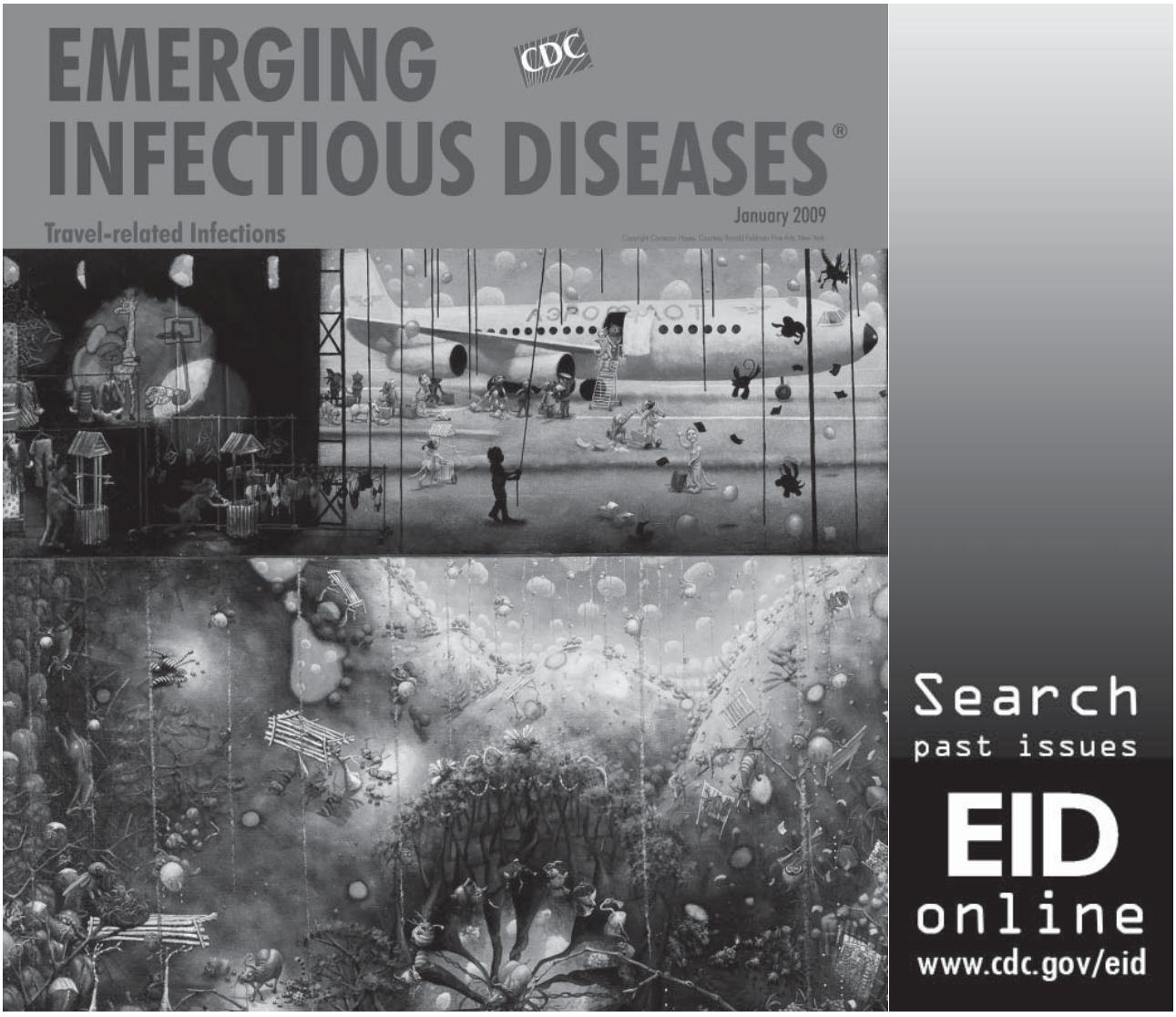

Tropical Diseases in Travelers

Eli Schwartz, editor

Wiley-Blackwell, Chichester, UK, 2009
ISBN: 9781405184410
Pages: 485; Price: US $159.00

This book captures the essence of tropical medicine for clinicians evaluating returning travelers. The editor, an international expert in tropical and travel medicine, authored or coauthored many chapters of the book. The book also reflects the experience of numerous experts in the field of travel medicine.

The book consists of 43 chapters organized into 3 sections: general aspects of tropical diseases in travelers, specific infections, and approaches to specific syndromes. The first section describes general trends in travel medicine and discusses types of studies encountered in travel medicine research. This section provides a basis for screening travelers and makes recommendations for doing so.

The section on specific diagnoses dedicates a chapter each to the most commonly encountered groups of microbial organisms. This section emphasizes the epidemiology of travel illnesses and clinical signs and symptoms in travelers, especially aspects of illness different from those of populations residing in the disease-endemic areas. This section also includes photographs of physical findings in travelers; the photographs highlight such diseases as African tick-bite fever, chikungunya, dengue, swimmer's itch, African trypanosomiasis, leishmaniasis, measles, tungiasis, and cutaneous larva migrans.

The section on syndromes focuses on approaches to evaluating major complaints in returning travelers. Complaints discussed include posttravel diarrhea, fever, skin problems, eosinophilia, respiratory complaints, rheumatologic conditions, and neurologic findings.

For clinicians, adequate knowledge of illnesses associated with travel is critical to the ability to provide proper pretravel advice. This book contributes much information to assist in understanding diseases encountered by travelers. It is a valuable reference on tropical and travel medicine and is especially important to clinicians managing ill travelers. However, it also supplies fundamental background information for clinicians providing only pretravel consultations. The authors present concise, solid evidence and practical insights on tropical diseases in travelers. I recommend it highly to clinicians involved in the care of travelers in industrialized and developing countries.

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DOI: 10.3201/eid1511.091287

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Contagion and Chaos: Disease, Ecology, and National Security in the Era of Globalization

Andrew T. Price-Smith

Massachusetts Institute of Technology Press, Cambridge, MA, USA, 2009
ISBN: 978-0-262-66203-1
Pages: 296; Price: US $24.00 (paperback)

Contagion and Chaos describes the threat that emerging and reemerging infectious diseases pose to international security because of these diseases' negative effects on sovereign states. The author proposes the following 5 hypotheses: 1) epidemic disease may compromise the prosperity, legitimacy, structural cohesion, and, in certain cases, security of sovereign states; 2) epidemics and pandemics of emerging or reemerging infectious diseases may promote economic and political discord among countries but are unlikely to generate serious armed conflict; 3) only some pathogens threaten national security according to criteria such as lethality, transmissibility, fear, and economic damage; 4) warfare (intrastate and interstate) amplifies problems caused by disease; and 5) the paradigm of health security is philosophically grounded in the political tradition of republican theory.

The author stresses that the association between the health of a population and perception of national security is ancient but largely forgotten. He suggests that a republican revision of systems-level international relations theory provides an optimal framework for examining the paradigm of health security.

The book's 8 chapters discuss data supporting the author's hypotheses. The first chapter describes the relationships among pathogens, society, and the state from a political science perspective. For nonpolitical scientists, this chapter is difficult. However, chapters 2–7 are interesting and enlightening. Chapter 2 explores the historical relationship between the state and society in the context of contagion. The author provides a historical perspective for the long-held perception that infectious disease poses a distinct threat to the stability, prosperity, material interests, and, therefore, security of the state. Chapters 3–6 present case studies concerning the influenza pandemic of 1918, HIV/AIDS, bovine spongiform encephalopathy and its human variant, Creutzfeld-Jakob disease, and severe acute respiratory syn-

drome. Each illness is discussed in the context of disease-induced destruction and debilitation of the population, erosion of productivity and prosperity, fear-induced social destabilization, disruption of governance institutions, and the consequent erosion of state power relative to unaffected rival states. In Chapter 7, violent conflict and war are shown to be disease amplifiers through examination of the mechanisms by which interstate and intrastate conflict contributes to disseminating existing pathogens and to emerging novel microorganisms. The final chapter examines the proposition that health contributes to economic prosperity, which bolsters the power of the state. Each chapter has extensive notes to assist the reader.

The author proposes that the best way to curtail future epidemics (and pandemics) is to augment the healthcare infrastructure and improve the health of populations. Fulfilling these needs is particularly important for developing countries where conditions are favorable for disease emergence because of globalization that results in increased population density, ecological degradation, rapid transportation technologies, and mass migration and because of low or nonexistent disease surveillance and containment capacities. This book will be of interest to political scientists and those in public health and medicine because it highlights the interdependence between political science and public health.

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Outbreak Investigations around the World: Case Studies in Infectious Disease Field Epidemiology

Mark S. Dworkin

Jones and Bartlett Publishers, Inc., Sudbury, MA, USA, 2009
ISBN-10: 076375143X
Pages: 480, Price: US $64.95

Outbreak investigations are fascinating stories. Mark S. Dworkin, Epidemic Intelligence Service (EIS) Class of 1994, has compiled 19 first-hand accounts of case studies in infectious disease epidemiology and presents them in chronological order. The first is Kenrad Nelson's 1964 investigation of leptospirosis associated with swimming in an irrigation ditch in rural Washington; the last, Patricia Quinlisk's evaluation of a 2006 mumps epidemic in Iowa. In between are investigations involving 8 bacterial infections, 6 viruses, 1 helminth (*Taenia solium*), 1 protozoan (*Cryptosporidium* sp.), and a misdiagnosis of *Entamoeba histolytica*. Fourteen of the outbreaks occurred in the United States; of the remaining 5, one each occurred in Portugal, Israel, Egypt, Gabon, and Liberia.

In general, the stories are told as first-person accounts, use an informal style, and include personal reflections. Many chapters, but not all, include epidemic curves, maps, tables, exhibits, and lessons learned. I especially enjoyed reading about Paul Blake's experience with a cholera outbreak in Portugal, Charles Jennings and measles in Illinois, Daniel Bausch and Ebola in Gabon, and reading both chapters by Jeffrey Davis—toxic shock syndrome and cryptosporidiosis.

As an instructor of epidemiology, I read the book seeking a complementary text for students. The informal style does make enjoyable reading but does not translate into an appropriate textbook. Several of the chapters are too long. One chapter is written by multiple authors, told from 4 points of view, and is very difficult to read. The lessons learned are organized chronologically, not by content. Some lessons are redundant; other areas of epidemiology are not adequately explored, e.g., sampling strategies, study design, questionnaire development and data analysis, population screening, and noninfectious diseases. However, I like the concept of first-hand accounts to supplement epidemiology textbooks. Could one format the chapters as unknowns like that of New England Journal of Medicine case studies? Could outbreak investigations be written in the style of Berton Roueché as medical mysteries, but supplemented with epidemic curves, maps, and lessons learned?

I recommend this book to all infectious disease epidemiologists, EIS officers, and infectious diseases clinicians interested in the aura of outbreak investigations. I also encourage the editor to consider a reformatted second edition to enhance the book's usefulness as a complementary text in epidemiology coursework.

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Unexpected

Veranja Liyanapathirana

He came in for a urethral job
TURP is what the doctor said
Nothing serious
He sought treatment because his son insisted
"What is it with getting up twice at night?"
"No Thaththa,[1] it'll be a safe surgery"
"OK Putha,[2] you know the best"
For he was proud that his son was a nurse

The day dawned; he came to the ward,
With son and wife, and daughter to be
The harried young intern
Gave an uninterested look
"Routine admission, nothing much"
"BP normal, pulse regular, heart in dual rhythm"
"DT form filled, theatre list made"
Anaesthetist came for the premed
"Healthy gentleman, nothing to worry"
"Is there a slight murmur?"
"No, can't be, the HO would have heard"
Surgery goes well,
Recovery uneventful,
Bladder irrigation continued uneventfully.
His son the nurse and daughter to be the nurse
Were always there anyway, most of the
nurses were their friends
So things moved smoothly

Post op day 3
Fever spike
"Nothing to worry, just a UTI,
Change the antibiotic,
Send urine for culture"
The urologist said
A week went by,
Fever continued to spike
His son the nurse spoke to the urologist
"What can it be, Sir?"
"Nothing to worry, just a UTI"
"But the culture had no growth"
"He was on prophylactic antibiotics"
Day 10 came, He developed seizures,
"What can it be?"
"DVT with emboli shooting"
"Let's do a CT"
"CT normal"
"Get a duplex of lower limb"
"Also normal"
Fever continues
Poor man, felt so unwell
Just by chance
Another intern kept the steth on his chest
"Oh my god, the murmur of MR"
"Take blood cultures"
"Do CRP"
"Get an Echo done"

On the way to the echo room, his left side goes numb
"Oscillatory vegetation in mitral valve"
"Start Pen and Gen"
Next day comes,
"MRSA isolated from blood cultures"
The dreaded report
Now what to give?
"Call the microbiologist"
"It has usually got a bad prognosis"
"Call the cardiologist"
Arguments, consultations
In the midst of it,
His son looks helpless
"Why did I push Thaththa to undergo surgery?"

The father looks on
Oblivious to the commotion
But deep within
He knows
That something's not right
"My son's wedding
My wife's future"
He thinks……

Dr Liyanapathirana is a lecturer in the Department of Microbiology, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka. Her research interests include rickettsial infections and molecular microbiology.

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[1]Father

[2]Son

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Romare Bearden (1911–1988) Circe Turns a Companion of Odysseus into Swine (1977) Collage of papers with paint and graphite on fiberboard (81.3 cm × 111.8 cm) Copyright Romare Bearden Foundation/Licensed by VAGA, New York, NY, USA

Put Me in the Sky[1]

Polyxeni Potter

"I thought that I was going to be a doctor, and I majored in science and later in mathematics. But when I got out of college, I decided to study art," divulged Romare Bearden in a 1968 oral history interview. In New York, "I went to study with George Grosz at the Art Students League." The German-born artist guided Bearden's understanding of draftsmanship and classical technique, introducing him to Ingres, Hogarth, Holbein, and Dürer and urging him to "really observe."

"I was born in Charlotte, North Carolina …. I grew up mostly in New York and some time in Pittsburgh, where I would go to see my grandmother," Bearden said about his peripatetic childhood. But he added on another occasion, "I never left Charlotte except physically." His family, part of the Great Migration north to escape racial segregation, became prominent in their new community, sharing in the intellectual, artistic, and political mainstream of the 1920s and '30s cultural movement, Harlem Renaissance.

"When I finished studying with Grosz, I drew at home and I got a job as a political cartoonist." But painting was what he wanted to do, so he got a studio in New York, same building as Jacob Lawrence and other artists, writers, and musicians, who became his friends. "I began at that time to do my Southern themes, the people that I'd seen as a young boy when I'd sometimes visit North Carolina …." This promising career was interrupted by World War II, when he joined the army.

"After the war, I began to arrive at some kind of personal identification." Like many in his circle, he traveled to France, "Paris was just like a thing of dreams to me." But despite his fascination with the city and the people he met, among them Georges Braque and Constantin Brâncuşi, he did not paint at all there. Back in New York, he gradually overcame his desire to return to Paris and started to paint again, experimenting with color "not as decoration" but as "form, as space," with "flat painting, shallow space, Byzantine stylization, and African design."

"I think the artist has to be something like a whale, swimming with his mouth wide open, absorbing everything until he has what he really needs." Bearden dabbled in many techniques and media, enriching them with his understanding of literature, music, and philosophy. He wrote successfully and had to be dissuaded from pursuing music so that he would remain focused on art. He grew up listening to Duke Ellington's orchestra and Ella Fitzgerald's singing. For 16 years, his studio was above the Apollo Theater, a Harlem landmark. "I paint out of the tradition of the blues," he wrote. "The more I played around with visual notions as if I were improvising like a jazz musician, the more I realized what I wanted to do as a painter, and how I wanted to do it."

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[1]Short story by Eudora Welty, later retitled "Circe."

In the 1960s, he moved away from painting toward more structured and varied compositions that better accommodated his conflicting interests in representation and abstraction. His richly textured collages, which captured every aspect of that turbulent era, contained, among other bits and pieces, painted images from other art works or photostatic enlargements made from photographs of these works. These enlargements, or Projections as they were called, featured in spectacularly complex works that synthesized old and new concepts: Manet's Olympia in the Civil Rights Era, Matisse in rural North Carolina, Poseidon in New York. "I try to show that when some things are taken out of the usual context and put in the new, they are given an entirely new character."

During the latter part of his life, Bearden often visited the Caribbean island of St. Martin. There he explored in depth a favored theme: human migration and the search for home. Near the water, for him a source of energy, he conceived his Odysseus series, 20 large collages and other smaller works inspired by Homer's epic recounting the hero's 10-year quest for Ithaca on the way back from the Trojan War.

"How you have gotten it! It's all here, all right," wrote Nobel Laureate Derek Walcott in his poem, "To Romare Bearden," praising the artist's genius and his ability to project humanity in visual, plastic terms. Intrigued by the universality of Homeric themes and their applicability to pressing issues of all time, the artist painted them with vigor and wit. "I am trying to explore, in terms of the particulars of the life I know best, those things common to all cultures."

In Circe Turns a Companion of Odysseus into Swine, on this month's cover, Bearden revisits this episode in the Odyssey with the clarity of a draftsman and the elusiveness of a storyteller. His view is theatrical, the luscious set strewn with clues. At Circe's palatial edifice in the forest glade, the sky is brilliant against a slice of pink and a window curtain blowing in the breeze. At center stage, the goddess approaches an intruder. Face whiskered, arm snaked, she is poised to strike, has already, man into swine. Lawn and forest are littered with birds. In this flat sea of static figures, Bearden navigates beauty, magic, horror.

Circe "of the braided tresses" and her island, a major stop on Odysseus' crowded itinerary, have had many interpretations. This granddaughter of the sun, goddess, enchantress who transforms men into animals and birds, cajoles the crew into a prolonged unscheduled stop and then, reluctantly, guides the hero's exit to the sea. "Don't evade, don't pretend you won't leave after all: you leave in the story and the story is ruthless," laments Canadian author Margaret Atwood's Circe, the one left behind.

"Needle in air, I stopped what I was making," the goddess reports in Eudora Welty's version of the episode, alluding to Odysseus' arrival, her hospitality, the loom, the kitchen, the garden, the beauty of the island. This archetypal female character is entangled in the essence of Homer's epic: the yearning for freedom and immortality that puts humans on paths riddled with danger and death. "Put me in the sky," Welty's Circe asserts, following the story line, frustrated with the turn of events. She wants to escape, become a distant constellation. I could have had "a ship too," she professes, "if I were not tied to my island, as Cassiopeia must be to sticks and stars of her chair."

Odysseys trace the paths of human migration: escape from war or segregation, poverty and famine; exploration of the earth and beyond; restlessness and search for meaning; hearth and harbor—the circuitous return to Ithaca, what a school of lessons! Magic and horror dominate. Dangers lurk en route. In our "Projection after Bearden," this issue alone, they rival any epic's: pandemic (H1N1) 2009, imported poliomyelitis, hepatitis A, Buruli ulcer, Mayaro fever, melioidosis, spreading multidrug-resistant TB, gastroenteritis at tourist resorts, dengue fever, malaria in refugees, low immunity to measles and rubella among guest workers, hepatitis E caused by a virus thought to come from pigs in the first outbreak reported on a cruise ship.

Not the least of plagues emerging around the globe are zoonotic infections due, not to travel by the animals so much as to their indiscriminate trade by humans. But even this twist is not beyond the scope of ancient epics. "It's the animals I'm afraid of," warned Atwood's Circe, turning Odysseus' story on its ear, "... they may transform themselves back into men."

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EMERGING INFECTIOUS DISEASES

Upcoming Issue

Virulence Factors and Possible Control of *Streptococcus iniae* in Fish

Genomic Signatures of Influenza A Pandemic (H1N1) 2009 Virus

Cost-effectiveness of Hospital Infection Control Response to an Epidemic Respiratory Virus Threat

Tick-borne Agents in Rodents, China, 2004–2006

Novel Calicivirus in Rabbits, Michigan, USA

Circulation of Distinct *Anaplasma phagocytophilum* Genotypes and Vector Specificity

Possible Interruption of Malaria Transmission, Highland Kenya, 2007–2008

Community-associated Methicillin-Resistant *Staphylococcus aureus* in Outpatients, United States, 1999–2006

Highly Pathogenic Avian Influenza Virus (H5N1) in Backyard Chickens, Bangladesh

Genetic Analysis of *Francisella tularensis* Isolates from Humans, Sweden

Antiviral Drug–Resistant Influenza A in Long-Term Care Facility, Illinois, USA, 2008

Mopeia virus–related Arenavirus in Natal Multimammate Mice, Tanzania

Human Trichinellosis after Consumption of Soft-Shelled Turtles, Taiwan

Transplacental Transmission of Bluetongue Virus 8 in Cattle, UK

New Adenovirus in Bats, Germany

Oseltamivir-Resistant Influenza A Pandemic (H1N1) 2009 Virus, Hong Kong, China

Cross-Sectional Survey of Hantavirus Infection, Brazil

Echinococcus vogeli Infection in a Hunter, French Guiana

Bartonella rochalimae in Raccoons, Coyotes, and Red Foxes

Complete list of articles in the December issue at http://www.cdc.gov/eid/upcoming.htm

Upcoming Infectious Disease Activities

November 7–11, 2009
American Public Health Association's 137th Annual Meeting and Exposition
Philadelphia, PA, USA
http://www.apha.org/meetings

November 18–22, 2009
American Society of Tropical Medicine and Hygiene 58th Annual Meeting
Marriott Wardman Park
Washington, DC, USA
http://www.astmh.org/meetings/index.cfm

December 4–6, 2009
Northeastern Ohio Universities Colleges of Medicine and Pharmacy
27th Annual Infectious Disease Seminar for the Practicing Physician
Edgewater Beach Hotel
Naples, FL, USA
http://www.neoucom.edu/ce

2010

February 19–21, 2010
2nd International Berlin Bat Meeting: Bat Biology and Infectious Diseases
Berlin, Germany
http://www.izw-berlin.de

March 18–22, 2010
Fifth Decennial: International Conference on Healthcare-Associated Infections 2010
Hyatt Regency Atlanta
Atlanta, GA, USA
http://www.decennial2010.com

March 24–26, 2010
16th ISHEID (International Symposium on HIV & Emerging Infectious Diseases)
Marseille, France
http://www.isheid.com

Announcements

To submit an announcement, send an email message to EIDEditor (eideditor@cdc.gov). In 50–150 words, describe timely events of interest to our readers. Include the date of the event, the location, the sponsoring organization(s), and a website that readers may visit or a telephone number or email address that readers may contact for more information.

Announcements may be posted on the journal Web page only, depending on the event date.

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Article Title

Multicenter GeoSentinel Analysis of Rickettsial Diseases in International Travelers, 1996–2008

CME Questions

1. Which of the following are no longer classified as rickettsial disorders?

A. *Ehrlichia* and *Anaplasma*
B. *Orientia* and *Coxiella burnetti*
C. *Coxiella burnetti* and *Bartonella*
D. *Anaplasma* and *Bartonella*

2. A 44-year-old male traveler returning from Tanzania presents 7 days after return with fever and respiratory symptoms. Among rickettsial diseases to be considered, which of the following is most likely to be the cause of his illness?

A. Ehrlichiosis
B. Spotted fever group rickettsiosis
C. Bartonellosis
D. Typhus group rickettsiosis

3. Which of the following is least likely to be positively and independently associated with spotted fever group rickettsiosis in a returning international traveler?

A. Travel for business
B. Visit to southern Africa
C. Male gender
D. Travel from March to May

4. Which of the following is the most commonly used treatment for rickettsial disease among returning international travelers?

A. Tetracycline
B. Minocycline
C. Septra
D. Doxycycline

Activity Evaluation

1. The activity supported the learning objectives.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly Disagree				Strongly Agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly Disagree				Strongly Agree
1	2	3	4	5

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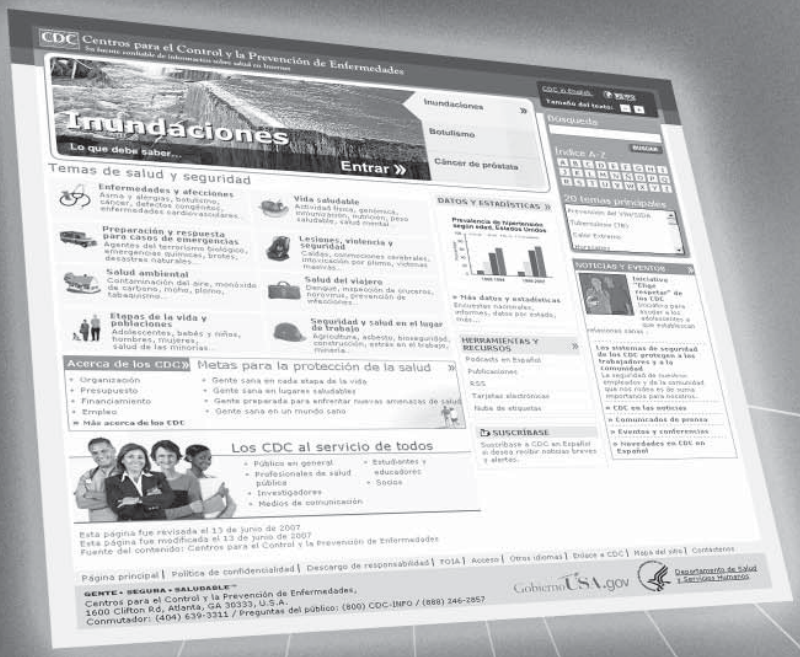

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R S T U V W X Y Z

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Enfermedades y afecciones
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Preparación y respuesta para casos de emergencias
Agentes del terrorismo biológico, emergencias químicas, brotes, desastres naturales...

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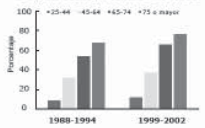

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EMERGING INFECTIOUS DISEASES

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JOURNAL BACKGROUND AND GOALS

What are "emerging" infectious diseases?

Infectious diseases whose incidence in humans has increased in the past 2 decades or threatens to increase in the near future have been defined as "emerging." These diseases, which respect no national boundaries, include

- New infections resulting from changes or evolution of existing organisms.
- Known infections spreading to new geographic areas or populations.
- Previously unrecognized infections appearing in areas undergoing ecologic transformation.
- Old infections reemerging as a result of antimicrobial resistance in known agents or breakdowns in public health measures.

Why an "Emerging" Infectious Diseases journal?

The Centers for Disease Control and Prevention (CDC), the agency of the U.S. Public Health Service charged with disease prevention and health promotion, leads efforts against emerging infections, from AIDS, hantavirus pulmonary syndrome, and avian flu, to tuberculosis and West Nile virus infection. CDC's efforts encompass improvements in disease surveillance, the public health infrastructure, and epidemiologic and laboratory training.

Emerging Infectious Diseases represents the scientific communications component of CDC's efforts against the threat of emerging infections. However, even as it addresses CDC's interest in the elusive, continuous, evolving, and global nature of these infections, the journal relies on a broad international authorship base and is rigorously peer-reviewed by independent reviewers from all over the world.

What are the goals of Emerging Infectious Diseases?

1) Recognition of new and reemerging infections and understanding of factors involved in disease emergence, prevention, and elimination. Toward this end, the journal

   - Investigates factors known to influence emergence: microbial adaptation and change, human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, and the breakdown of public health measures.
   - Reports laboratory and epidemiologic findings within a broader public health perspective.
   - Provides swift updates of infectious disease trends and research: new methods of detecting, characterizing, or subtyping pathogens; developments in antimicrobial drugs, vaccines, and prevention or elimination programs; case reports.

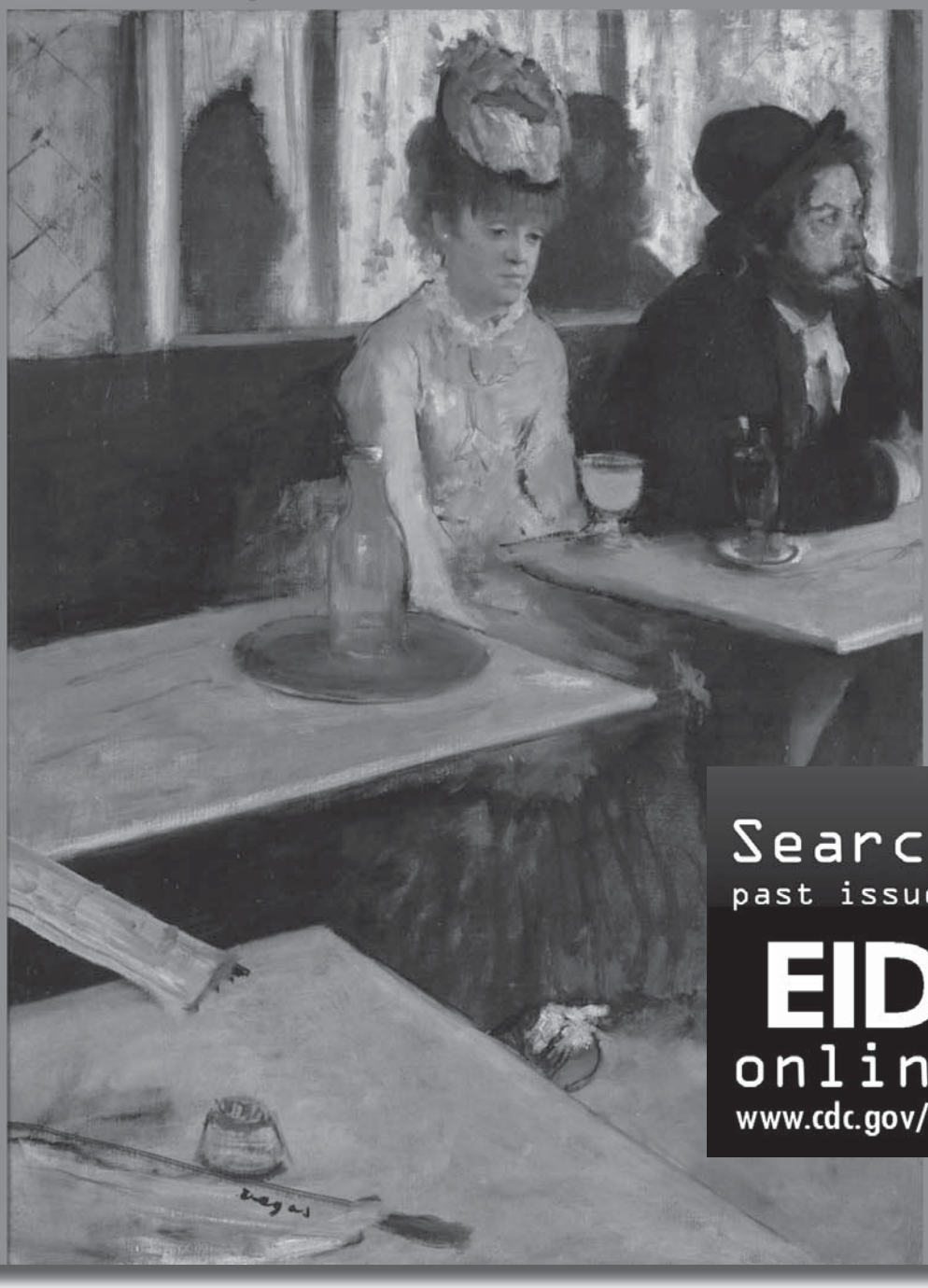
2) Fast and broad dissemination of reliable information on emerging infectious diseases. Toward this end, the journal

   - Publishes reports of interest to researchers in infectious diseases and related sciences, as well as to public health generalists learning the scientific basis for prevention programs.
   - Encourages insightful analysis and commentary, stimulating global interest in and discussion of emerging infectious disease issues.
   - Harnesses electronic technology to expedite and enhance global dissemination of emerging infectious disease information.

EMERGING INFECTIOUS DISEASES®

October 2009

Nontuberculous Mycobacteria



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Emerging Infectious Diseases is a peer-reviewed journal established expressly to promote the recognition of new and reemerging infectious diseases around the world and improve the understanding of factors involved in disease emergence, prevention, and elimination.

The journal is intended for professionals in infectious diseases and related sciences. We welcome contributions from infectious disease specialists in academia, industry, clinical practice, and public health, as well as from specialists in economics, social sciences, and other disciplines. Manuscripts in all categories should explain the contents in public health terms. For information on manuscript categories and suitability of proposed articles see below and visit www.cdc.gov/eid/ncidod/ EID/instruct.htm.

Emerging Infectious Diseases is published in English. To expedite publication, we post articles online ahead of print. Partial translations of the journal are available in Japanese (print only), Chinese, French, and Spanish (www.cdc. gov/ncidod/EID/trans.htm).

Instructions to Authors

Manuscript Preparation. For word processing, use MS Word. List the following information in this order: title page, article summary line, keywords, abstract, text, acknowledgments, biographical sketch, references, tables, figure legends, appendixes, and figures. Each figure should be in a separate file.

Title Page. Give complete information about each author (i.e., full name, graduate degree(s), affiliation, and the name of the institution in which the work was done). Clearly identify the corresponding author and provide that author's mailing address (include phone number, fax number, and email address). Include separate word counts for abstract and text.

Keywords. Include up to 10 keywords; use terms listed in Medical Subject Headings Index Medicus.

Text. Double-space everything, including the title page, abstract, references, tables, and figure legends. Indent paragraphs; leave no extra space between paragraphs. After a period, leave only one space before beginning the next sentence. Use 12-point Times New Roman font and format with ragged right margins (left align). Italicize (rather than underline) scientific names when needed.

Biographical Sketch. Include a short biographical sketch of the first author—both authors if only two. Include affiliations and the author's primary research interests.

References. Follow Uniform Requirements (www.icmje.org/index.html). Do not use endnotes for references. Place reference numbers in parentheses, not superscripts. Number citations in order of appearance (including in text, figures, and tables). Cite personal communications, unpublished data, and manuscripts in preparation or submitted for publication in parentheses in text. Consult List of Journals Indexed in Index Medicus for accepted journal abbreviations; if a journal is not listed, spell out the journal title. List the first six authors followed by "et al." Do not cite references in the abstract.

Tables. Provide tables within the manuscript file, not as separate files. Use the MS Word table tool, no columns, tabs, spaces, or other programs. Footnote any use of boldface. Tables should be no wider than 17 cm. Condense or divide larger tables. Extensive tables may be made available online only.

Figures. Provide figures as separate files, not embedded in MS Word. Use Arial font for text content. Place keys within figure area. Provide footnotes and other information (e.g., source/copyright data, explanation of boldface) in figure legend. Submit figures with text content in native, editable, PC file formats (e.g., MS Excel/PowerPoint). Submit image files (e.g., electromicrographs) without text content as high-resolution (300 dpi/ppi minimum) TIFF or JPG files. Submit separate files for multiple figure panels (e.g., A, B, C). EPS files are admissible but should be saved with fonts embedded (not converted to lines). No PNG or BMP files are admissible. For additional guidance, contact fue7@cdc.gov or 404-639-1250.

Manuscript Submission. Include a cover letter indicating the proposed category of the article (e.g., Research, Dispatch) and verifying that the final manuscript has been seen and approved by all authors. Complete provided Authors Checklist. To submit a manuscript, access Manuscript Central from the Emerging Infectious Diseases web page (www.cdc.gov/eid).

Types of Articles

Perspectives. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and a brief biographical sketch. Articles in this section should provide insightful analysis and commentary about new and reemerging infectious diseases and related issues. Perspectives may also address factors known to influence the emergence of diseases, including microbial adaptation and change, human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, and the breakdown of public health measures. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Synopses. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and a brief biographical sketch. This section comprises concise reviews of infectious diseases or closely related topics. Preference is given to reviews of new and emerging diseases; however, timely updates of other diseases or topics are also welcome. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Research Studies. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary, and a brief biographical sketch. Report laboratory and epidemiologic results within a public health perspective. Explain the value of the research in public health terms and place the findings in a larger perspective (i.e., "Here is what we found, and here is what the findings mean").

Policy and Historical Reviews. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words), a one-sentence summary of the conclusions, and a brief biographical sketch. Articles in this section include public health policy or historical reports that are based on research and analysis of emerging disease issues.

Dispatches. Articles should be no more than 1,200 words and need not be divided into sections. If subheadings are used, they should be general, e.g., "The Study" and "Conclusions." Provide a brief abstract (50 words); references (not to exceed 15); figures or illustrations (not to exceed 2); tables (not to exceed 2); and a brief biographical sketch. Dispatches are updates on infectious disease trends and research. The articles include descriptions of new methods for detecting, characterizing, or subtyping new or reemerging pathogens. Developments in antimicrobial drugs, vaccines, or infectious disease prevention or elimination programs are appropriate. Case reports are also welcome.

Commentaries. Thoughtful discussions (500–1,000 words) of current topics. Commentaries may contain references but no figures or tables.

Another Dimension. Thoughtful essays, short stories, or poems on philosophical issues related to science, medical practice, and human health. Topics may include science and the human condition, the unanticipated side of epidemic investigations, or how people perceive and cope with infection and illness. This section is intended to evoke compassion for human suffering and to expand the science reader's literary scope. Manuscripts are selected for publication as much for their content (the experiences they describe) as for their literary merit.

Letters. Letters commenting on recent articles as well as letters reporting cases, outbreaks, or original research are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have 1 figure or table and should not be divided into sections. All letters should contain material not previously published and include a word count.

Books, Other Media. Reviews (250–500 words) of new books or other media on emerging disease issues are welcome. Name, publisher, number of pages, other pertinent details should be included.

Announcements. We welcome brief announcements (50–150 words) of timely events of interest to our readers. (Announcements may be posted online only, depending on the event date.)

Conference Summaries. Summaries of emerging infectious disease conference activities are published online only. Summaries, which should contain 500–1,000 words, should focus on content rather than process and may provide illustrations, references, and links to full reports of conference activities.