First Case of Human Ehrlichiosis in Mexico

To the Editor: Ehrlichiosis is a zoonotic disease transmitted to humans through the bite of infected ticks (1). The first recognized human ehrlichial infection, Sennetsu fever, was described in Japan in 1954 (2). The first case of human ehrlichiosis in the United States was recognized in 1986 and was reported in 1987 (3). The disease is caused by intracellular gram-negative bacteria of the *Ehrlichia* genus. The bacteria can be found in the monocytes and granulocytes of peripheral blood. Human monocytic ehrlichiosis is caused by *E. chafeensis,* and human granulocytic ehrlichiosis is caused by *E. equi* or *E. phagocytophilia,* which was first recognized in 1994 (4). Most cases occur between April and September, and the reservoirs are field animals such as rodents, deer, and dogs. The clinical spectrum of the disease is similar to that of other febrile illnesses; without adequate and timely treatment, approximately 5% of the patients die (5).

In the United States, more than 400 cases of serologically confirmed *E. chaffensis* infection have been documented since 1996 (6). No cases have been reported in Mexico.

In February 1997, we evaluated a 41-year-old male patient from Merida. The patient had been exposed to ticks during activity in a rural area 1 week before the onset of illness. Clinical manifestations included frequent hyperthermia, rash, myalgia, headache, anorexia, fatigue, and cough. Physical examination showed bilateral cervical lymphadenopathy, and a chest radiograph showed an interstitial bilateral infiltrate. Hematic cytometry showed thrombocytopenia of 134 x $10^3/\mu L$ and 3200 leukocytes (1440 neutrophils/μL). Hepatic transaminases were elevated, with an aspartate aminotransferase: 92 U/L (normal: 22 U/L), alanine aminotransferase: 48 U/L (normal: 18 U/L), gamma-glutamyltranspeptidase: 278 U/L (normal: 28 U/L); and globulins: 4.8 g/dL with a polyclonal pattern. No antibodies against rickettsia, dengue virus, B-19 parvovirus, or HIV were detected. A serum sample gave a positive reaction by indirect immunofluorescence assay against *E. chaffeensis* at titers of 1:64 on week 2 and 1:128 on week 3. No infected monocytes or granulocytes were observed in peripheral blood. Remission of the clinical manifestations began on week 4 and was completed on week 6.

This case indicates the existence of human ehrlichiosis in Yucatan, Mexico. Reactivity to *E. chaffeensis* suggests human monocytic ehrlichiosis; however, as antibody testing was not performed with *E. phagocytophila* or *E. equi,* the possibility of human granulocytic ehrlichiosis cannot be excluded. In any event, case reports indicate the need for deliberate search for cases. Dengue is endemic in this area of Mexico, and ehrlichiosis should be considered as a differential diagnosis.

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HIV-1 Subtype F in Single and Dual Infections in Puerto Rico: A Potential Sentinel Site for Monitoring Novel Genetic HIV Variants in North America

To the Editor: Although international efforts to systematically collect, characterize, and classify HIV isolates from around the world have increased considerably, data on HIV-1 genetic variations in Puerto Rico are limited. This island (population 3.7 million) has one of the highest

AIDS incidence rates in the United States (53.3 cases per 100,000) (1). To evaluate the potential for a multiple subtype distribution pattern in Puerto Rico, we analyzed genetic variations between HIV-1 strains isolated from peripheral blood mononuclear cells of 63 asymptomatic HIV-infected female commercial sex workers from 12 communities. These participants were part of 290 female commercial sex workers followed in a larger cross-sectional study of risk behavior (2).

HIV-1 subtypes F (n = 4) and B (n = 44) strains were identified in persons infected with a single viral subtype with a molecular screening assay based on restriction fragment length polymorphism (RFLP) analysis and with DNA sequencing of the viral protease gene-prot (3). The remaining 15 specimens were classified by RFLP as potential dual infections. Further cloning and sequencing of prot from three of these specimens confirmed one dual infection involving subtypes F and B viruses and identified two infections caused by genetically distinct quasispecies of subtype B variants.

In further detailed pairwise analysis of HIV-1 prot genes, a small nucleotide divergence of 0.3% (0.0 to 1.1) within subtype F contrasted with a typical value of 6.3% (5.1 to 7.8) for the intrasubtype distance within subtype B prot sequences (4). The 99% similarity between prot subtype F Puerto Rican sequences suggested an epidemiologic link or a recent introduction of subtype F in Puerto Rico. Comparative sequence analysis of the C2-V3 env is useful in establishing the time that elapsed from infection on the basis of an annual nucleotide divergence of 0.5% to 1% in this region (5). Such analysis has been used to study the epidemiologic link between cases (4,6). Thus, we compared env sequences from two of five persons infected with prot subtype F strains. This analysis provided several observations. Env nucleotide divergence of 13.2% did not support a direct epidemiologic link between these strains. Furthermore, the relatively high intrasubtype diversity between env sequences suggested that evolution from a common progenitor would have taken a minimum of approximately 13 years. Phylogenetic analysis classified these two env sequences as subtype B, indicating that at least some of Puerto Rican prot subtype F viruses represent HIV-1 mosaics involving closely related prot F and significantly divergent env B sequences. Overall, discrepancy in both subtype assignment and nucleotide diversities within prot and env regions may indicate that distinct F/B mosaics circulating in Puerto Rico were likely the result of recombination between highly homogeneous subtype F of relatively recent arrival and divergent resident subtype B viruses.

HIV-1 infections with subtype F strains including B/F mosaics have been reported in Brazil (3,7). To evaluate a potential HIV-1 linkage between Brazil and Puerto Rico, a comparative phylogenetic analysis was done on subtype F viral prot sequences from these countries. This analysis documented that HIV-1 subtype F strains in Puerto Rico are distinct from both Brazilian and Romanian viruses. Furthermore, our results show that genetic analysis of prot allows tracking of subtype F viruses of different origin. Recently, by this approach, HIV-1 prot subtype F of Puerto Rican origin and F prot/B env mosaic were identified in HIV-1-infected persons in New York city (8). Observation of HIV-1 subtype F strains in Puerto Rico together with the recent report describing the first cases of such infections in New York indicates the potential for further emergence of subtype F on the North American continent. The presence of a complex distribution pattern of subtype F infections in Puerto Rico has serious implications for the evaluation and development of HIV diagnostics and vaccines.

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The nucleotide HIV-1 sequences obtained in this study were submitted to GenBank; their accession numbers are AF096813-AF096833.

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Paratyphoid Fever in India: An Emerging Problem

To the Editor: Enteric fever is a major public health problem in India, accounting for more than 300,000 cases per year, *Salmonella typhi* is the most common etiologic agent (1), but *Salmonella paratyphi A,* the other causative agent, causes more asymptomatic infections than *S. typhi*. According to earlier reports from India, *S. paratyphi A* was implicated as a causative agent in 3%-17% of enteric fever cases (2). However, a large community-based study in an urban slum of Delhi during October 1995 to October 1996 found that *S. paratyphi A* caused approximately 20%-25% of the cases of enteric fever in this region (3). An outbreak of enteric fever due to a single *S. paratyphi A* strain in an urban residential area was reported in 1996 from New Delhi, where contaminated water was implicated as the probable source (4,5). This outbreak prompted a retrospective analysis of the laboratory records of the All India Institute of Medical Sciences, New Delhi, over a 5-year period (1994-1998) to study the change, if any, in the etiology of enteric fever in North India.

We evaluated all blood culture records from the institute's clinical bacteriology laboratory for April to October (the months with the highest number of enteric fever cases) each year. Records were from patients residing in New Delhi and the surrounding areas of North India. The blood was collected by a phlebotomist in the outpatient department or by a resident doctor in hospital wards. Blood cultures were carried out by standard laboratory technique (6). Five ml of blood was added to 50 ml of brain heart infusion broth (Hi-Media Laboratory, India) under aseptic conditions. Bacterial identification was accomplished by standard microbiologic protocol (6). Susceptibility to antibiotics (amoxycillin, chloramphenicol, cotrimoxazole, gentamicin, ciprofloxacin, and ceftriaxone) was tested by the comparative disk diffusion method (Stokes method) (7). Chi-square for trend was calculated, and the p value was determined.

The total number of blood cultures performed for enteric fever cases (10,109 in 1994, 12,092 in 1995, 17,652 in 1996, 15,997 in 1997, and 17,012 in 1998) did not change significantly over this period. The isolation of *S. typhi* changed little (Chi-square = 2.367; p = 0.123; statistically not significant). However, the proportion of *S. paratyphi A* isolates rose from 6.5% in 1994 to 44.9% in 1998 (Chi-square = 22.20; p <0.001; statistically significant). The proportion of *S. paratyphi A* isolations in enteric fever cases from 1994 to 1998 was 6.5%, 21.2%, 50.5%, 30.7%, and 44.9%, respectively. Even excluding the strains from the 1996 outbreak (4), we found that the proportion of *S. paratyphi A* in enteric fever cases increased compared with *S. typhi* (Chi-square = 30.528; p <0.001). With our catchment area, case definition of enteric fever, and laboratory methods remaining the same during this period, it appears that the etiology of enteric fever in North India is changing significantly.

The age-wise distribution of *S. typhi* and *S. paratyphi A* showed that *S. typhi* was a significant isolate from children < 5 years of age, while this distribution was not observed for *S. parathyphi A,* which involved those > 5 years of age. Sex was not significantly associated (mean male to female sex ratio was 32.4:18 for *S. typhi* and 15.8:10.6 for *S. paratyphi A*).

S. typhi has become increasingly sensitive to amoxycillin, chloramphenicol, and gentamicin, increasing from 75.1% in 1994 to 96.6% in 1998 for amoxycillin, from 71.9% in 1994 to 91.6% in 1998 for chloramphenicol, and from 96.4% to 100% for gentamicin. *S. paratyphi A* strains have remained uniformly sensitive (100%) to all antibiotics (amoxycillin, chloramphenicol, and gentamicin, as well as ciprofloxacin and ceftriaxone) used in the treatment of enteric fever. In light of reports of multidrug resistance in *S. typhi,* especially to quinolones, continued surveillance and monitoring of antimicrobial sensitivity of *S. paratyphi A* strains are needed.

The increase in proportion of *S. paratyphi* A cases, which may be due to a high degree of clinical suspicion (with mild fever cases investigated for enteric fever), changing host susceptibility, or even change in the virulence of the organism, should be further investigated.

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Hepatitis C Virus RNA Viremia in Central Africa

To the Editor: Epidemiologic serosurveys have demonstrated high prevalence (6%-15%) of hepatitis C virus (HCV) infection in adults in sub-Saharan Africa (1-4). Although possible false-positive HCV serologic test results have been reported in Africa, HCV prevalence rates suggest a high rate of chronic infection among persons with anti-HCV antibodies (5,6). We have focused on HCV RNA infectivity of blood from donors attending the National Blood Center in Bangui, Central African Republic.

We prospectively tested all blood donors between February and April 1998 for serum anti-HCV antibodies by both an HCV third-generation enzyme-linked immunosorbent assay (ELISA) (Abbott HCV EIA 3.0 test, Abbott, Chicago, IL, USA), which was chosen as a reference test for immunoglobulin (Ig) G antibodies to HCV, and by a simple membrane immunoassay system (Ortho HCV Ab Quik Pack, Ortho Diagnostic Systems Inc., Tokyo, Japan) (7). Anti-HCV-positive serum samples were further subjected to qualitative detection of HCV RNA by reverse transcription-polymerase chain reaction (AMPLICOR-HCV, Roche Diagnostic Systems, Inc., Branchburg, NJ, USA) (8). Of 163 serum samples (mean age ± standard deviation, 30±8 years), 155 were from male blood donors, 83 (51%) from first-time donors, and 125 (77%) from donors in the recipient's family. Fifteen (9.2%; 95% confidence interval [CI] 5%-15%) samples contained IgG to HCV by ELISA. Of the ELISA-positive samples, 14 were positive by the Quik Pack assay (sensitivity, 93.0%); of the 148 remaining ELISA-negative samples, 147 were negative by the Quik Pack assay (specificity, 99.3%). The agreement between the results of the two methods was 98.7%. Of the 163 samples, 10 (6.1%; CI 95%: 3%-11%) were positive for HCV antibodies (by ELISA and rapid test) and for HCV RNA.

We confirmed a high prevalence of HCV-seropositivity among blood donors in Bangui and the subsequent high rate of HCV RNA viremic blood donations. To offset the major risk for transfusion-acquired HCV in Central Africa we recommend screening donated blood for anti-HCV. When laboratory facilities to perform ELISA are not available, the Quik Pack system, a simple reliable method for detecting anti-HCV antibodies in human serum that requires neither complex reagent preparation nor expensive instrumentation, could prove useful.

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Immunization of Peacekeeping Forces[1]

To the Editor: The immunization status of military contingents arriving from different nations for peacekeeping missions may vary widely. This variation results from lack of information, coordination, and financial support.

For larger missions, the United Nations (UN) Headquarters issues recommendations about needed vaccines; recently, operations officers have consulted World Health Organization experts before issuing recommendations, and their advice, which takes into account epidemiologic data in the host country, has improved. Medical officers who develop recommendations for smaller missions must consider the pathogenic agent; environment; host efficacy, safety, and price of preventive measures; and legal and ethical aspects.

Data on the incidence of vaccine-preventable diseases within a military population that had similar duties in the same location are rarely available. When data from the respective region are not available, disease incidence or prevalence in the host country may be substituted. These data, however, may be misleading since the military often does not have the same lifestyle as the native population. Plague, for instance, had an incidence rate of 8 per 100,000 in Namibia, but not a single case was reported in the South African Armed Forces (unpub. SAMS report: Disease Profile of South West Africa, 1989). If epidemiologic documentation for a host country is not available, data from neighboring countries may be useful.

Traveler's diarrhea is the most frequent health problem abroad (1,2). Although the diarrhea is self-limited and lasts an average of 1 day with appropriate treatment (4 days without), the unproductive time may be detrimental to a military mission. Oral vaccines against the three most frequent causes of traveler's diarrhea (enterotoxigenic *Escherichia coli*, *Campylobacter* spp., and rotavirus [1,2]) are being developed; the latter will be available soon (3). Hepatitis A, most frequent among the vaccine-preventable diseases (4), is 10 to 100 times more frequent than typhoid fever (4,5). Hepatitis B occurs mainly in expatriates, but infections have also been observed in tourists who have had unprotected casual sex (6). The incidence rate of rabies is unknown, but animal bites that may result in rabies virus transmission and thus necessitate postexposure prophylaxis are frequent (7). Only anecdotal cases of diphtheria, tetanus, and tuberculosis have been reported (8). Poliomyelitis, yellow fever, Japanese encephalitis, and plague occur only in limited parts of the world (5). The situation may rapidly change as

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epidemics occur (e.g., diphtheria in eastern Europe in the early and mid-1990s) (9). If needed, the World Health Organization can provide information on confirmed and unconfirmed epidemics on a weekly basis.

Travel and peacekeeping mission statistics share similarities. In Namibia, the South African Armed Forces had most often observed hepatitis (unspecified), with rare cases of tuberculosis, typhoid, and meningitis (unpub. SAMS report: Disease Profile of South West Africa, 1989), as did the UN mission to Namibia, where within 12 months and with 7,114 employees, seven cases of hepatitis (mostly hepatitis A, some unspecified) occurred (10). No other vaccine-preventable infections were diagnosed in this UN mission.

Considering both risk (on the basis of incidence rates) and impact of infection, the priority for immunization (from highest to lowest) is as follows: hepatitis A, hepatitis B, rabies, poliomyelitis, yellow fever, typhoid fever, influenza, diphtheria, tetanus, meningococcal disease, Japanese encephalitis, cholera, and measles. To administer all vaccines would be extremely costly and may also result in an increased rate of adverse side-effects. Immunizations against the more frequent, more severe infections should be given priority.

If a mission is limited to one season, environmental factors of that respective season should be considered. This general rule is more important for vector-borne than for vaccine-preventable infections, except for influenza and meningococcal disease.

Persons who are already immune (because of previous immunization or immunity after infection) need not be vaccinated. The latter cause is particularly often true of hepatitis A; troops recruited in developing countries have an anti-hepatitis A virus seroprevalence rate close to 100% (11). Hepatitis B immunization, except for non- and low-responders, probably grants lifelong protection (12); the same is likely for measles vaccine.

Sometimes the host country may require proof of some specific vaccination based on the International Health Regulations (13), currently under fundamental revision to become a more effective tool in preventing the spread of infections that may be a global hazard (14).

In addition to adequate epidemiologic information and coordination between the military, international health organizations, and the host country, successful intervention efforts require thorough knowledge of vaccine characteristics with varying rates of efficacy and duration of protection. Cost-benefit evaluations, which would be very desirable, are unlikely in areas of political instability.

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Sexually Transmitted Diseases in Ukraine

To the Editor: With the political changes in eastern Europe in the last 10 years have come social and economic changes (1). Ukraine not only faces almost insurmountable problems as it tries to form a new government, it also faces many serious health issues including sexually transmitted diseases (STDs).

Surveillance data from the Ukrainian STD Center from January 1, 1989, through December 31, 1995, were analyzed on the basis of reports received through 1997. In western Europe, the incidence of syphilis and gonorrhea declined from 1980 to 1991 to less than 2% per 100,000 persons for syphilis and less than 20% per 100,000 persons for gonorrhea. However, in Ukraine, since 1989, the notification rate of syphilis has skyrocketed—from 5 per 100,000 persons in 1990 to 170 in 1995. In some regions, this rate exceeds 220 cases per 100,000 persons. Moreover, cases among children younger than 14 years of age are also increasing. In 1995, the syphilis rate for persons older than 30 years of age was 170 per 100,000; 600 per 100,000 girls younger than 15 years of age; and 1,550 to 2,000 per 100,000 girls 15 to 16 years of age. The large number of girls with the disease is in part due to teenage prostitution (1).

Most syphilis and gonorrhea cases are attributed to sexual transmission. Explanations of this phenomenon include the rapid growth of the sex industry, increasing numbers of homeless persons and refugees in Ukrainian cities, poor diagnostic facilities, punitive legislation that reduces the likelihood of going to treatment services, and limited or inadequate treatment (2).

The Ukrainian government is reviewing its arrangements for the control of STDs, including HIV/AIDS, to identify clear objectives and priorities. Education and treatment would be effective in preventing the spread of STDs in Ukraine, but these measures are inadequately funded (3). Evaluation and risk reduction are also great weapons in preventing the spread of STDs (4). However, the response of the local and world communities has been inadequate in stemming a major STD epidemic in Ukraine.

United Nation's Children's Fund (UNICEF) is developing a long-term program in Ukraine with a focus on STDs in adolescents and youth. This comprehensive program will tackle not only STDs but other related issues, such as HIV and teenagers' reproductive health (5).

Greater coordination of the agencies responsible for STD control in Ukraine will be sought, together with an expansion of health promotion and prevention projects for young persons and groups at high risk (6). An effective strategy for the control of STDs in Ukraine will, therefore, need to find ways to modify current programs and the way they interact to create effective control interventions.

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Yellow Fever Vaccine

To the Editor: Monath et al. (1) outlined existing facilities for distribution of yellow fever vaccines in the United States and pointed to difficulties for prospective vaccinees in remote locations. Their recommendation that primary health-care providers be allowed to dispense yellow fever vaccination merits serious consideration. Acceptance of such a strategy in the United States would inevitably be emulated elsewhere. Nevertheless, before such a strategy is approved, vaccine potency should be monitored at distribution points, and a sample of vaccine recipients should be examined for vaccine-induced immune response.

In Nigeria, systematic investigation of yellow fever vaccine distribution and transportation to remote locations has found loss in vaccine potency. Vaccine in storage sites and immunization centers in Lagos was fully potent, but potency in Osun and Oyo was 016 $\log_{10}$ to 0.22 $\log_{10}$ lower than the stipulated level (2). Furthermore, the titer of two vaccine lots that had been frozen after reconstitution from their lyophilized state dropped from the initial 3.15 $\log_{10}$ to 3.53 $\log_{10}$ to zero.

If the United States were to implement an extended strategy, similar studies of vaccine lots should be conducted to determine whether every vaccinee has received a full dose of yellow fever vaccine. In Illinois during the early 1970s, weak links in maintenance of refrigeration facilities and use of outdated vaccines in vials exposed to the sun for long hours were reported for live poliovirus vaccines (3). In the Northern Territory of Australia, examination of 144 vials of hepatitis B vaccine formulations during transport to immunization centers showed that 47.5% had been exposed to temperatures of -3°C or lower (4).

Assays of the potency of yellow fever vaccine, as well as quantification of vaccine-induced neutralizing antibody, is a multistep procedure that relies on inoculation of mice or Vero or polysaccharide cells (5). The successful "take" of yellow fever vaccine can be determined starting the second postvaccination day by demonstrable viremia detected by reverse-transcriptase polymerase chain reaction and by marked increases in neopterin, beta2-microglobulin, and circulating $CD8^+$ cells (6). Alternatively, elevated levels of tumor necrosis factor and interleukin-1 receptor antagonists on day two after vaccination (7) could be used to monitor the success of vaccinations by primary-care providers in remote areas in the United States (1) and elsewhere.

During the 1990s, isolation of yellow fever virus was reported in persons with a nonspecific febrile illness that did not meet the case definition of yellow fever (8). Air travel by such persons to the United States, which has areas infested by *Aedes aegypti,* could initiate yellow fever epidemics; because these travelers would have a nonspecific febrile illness, they would escape the existing surveillance network.

In conclusion, introducing yellow fever immunizations by primary health-care providers would be ideal, only with a concurrent plan to monitor vaccine potency at immunization centers and obtain in vitro evidence of a successful vaccine take. Such a strategy would blunt yellow fever–associated deaths, illnesses, and symptomless viral carriage in the community.

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Yellow Fever Vaccine—Reply to S. Arya

To the Editor: Dr. Arya correctly points out that there have been problems with degradation of live viral vaccines, including yellow fever vaccines, that have not been properly handled and stored at the point of use. However, in the United States and western Europe, yellow fever vaccines are stabilized and require the same storage facilities at the point of use as other vaccines routinely distributed by family physicians and pediatricians. Varicella vaccine (and even measles vaccine) is less stable than yellow fever vaccine but is distributed to all registered physicians in the United States. Since vaccines and other perishable medicines are typically shipped by overnight courier services using qualified methods that ensure maintenance of low temperature, there is no barrier to use of a similar system for yellow fever vaccine.

Empirical testing for antibody, viremia, or even surrogate markers of T-cell activation may be useful; however, it is difficult and expensive, involves unvalidated tests with unknown sensitivity and specificity, and is unnecessary, except under very special circumstances. A more direct measure of vaccine stability is direct potency measurement of samples stored at the point of use, as was done in the cited study in Nigeria by Adu et al. However, given the current controls on vaccine distribution in the United States, we do not believe that there would be a need to validate vaccine effectiveness at point of use in the event of a change of policy with respect to vaccinating centers. The cold-chain infrastructure and the training of medical personnel in vaccine storage and administration may not provide the same assurances in other countries. While our suggested changes to the system of yellow fever distribution may improve vaccine coverage and have other desirable benefits in the United States, they would not be appropriate for less stable systems for vaccine supply and use.

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