Vaccination in Travelers

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Vaccination of populations throughout the world has led to dramatic decreases in morbidity and mortality from many infectious diseases, including poliomyelitis and measles. In the United States, for example, morbidity and mortality from invasive disease from *Haemophilus influenzae* type b has decreased more than 99%. International travelers should ensure that they are up-to-date on their routine immunizations and then consider vaccination against other diseases based on risk. This article reviews new vaccines such as those against rotavirus, Lyme disease, and enterotoxigenic *Escherichia coli* and provides updated information on the risk of typhoid fever and the efficacy of vaccination against it. The use of hepatitis A vaccine in outbreak control, the safety of yellow fever vaccine, and the importance of protecting travelers against rabies exposure are also discussed. Vaccination is an important way for travelers to maintain their health before, during, and after travel.

Introduction

Vaccination for the prevention of travel-related illness is an important part of the health care of international travelers. Although much discussion during pretravel visits is spent on vaccines, in reality, the risk to an individual traveler of vaccine-preventable illness is usually far less than that of such other diseases as traveler's diarrhea, respiratory infection, and accidents or injuries. Nevertheless, the end of this decade is a particularly exciting time in vaccine technology and marks the introduction of several new products such as rotavirus, Lyme disease, and varicella vaccines; the development of combination vaccines; the use of new adjuvants to improve immunogenicity of other vaccines such as pneumococcal and meningococcal vaccines; novel vectors for vaccine delivery; and the anticipation of DNA vaccines. The new millennium should also see other vaccines targeted against chronic illness such as gastric ulcers caused by *Helicobacter pylori*.

The impact of vaccines has been profound on a population and global basis, with major advances in the control of many diseases in the United States and anticipated eradication of such other diseases as measles and poliomyelitis, which have been targeted by the World Health Organization (WHO). This review discusses important advances in vaccines used for travel (Table 1) as well as advances in the general field of immunization.

Childhood Immunization

Routine childhood immunization, which began in the United States in the mid-1950s, has led to either eradication or a decrease in incidence of over 99% in smallpox, diphtheria, poliomyelitis, measles, mumps, rubella, and *Haemophilus influenzae* type b infection (Table 2) [1••]. The last case of smallpox in the United States occurred in 1949; no cases of indigenously acquired wild-type polio have been reported since 1979; only 89 cases of measles were reported in the United States in 1998 (compared with over 500,000 annually from 1958 to 1962), with no deaths; and there has been a decline from 20,000 cases of invasive *H. influenzae* type b infection annually before 1990 to 125 cases in 1998. This remarkable achievement requires ongoing diligence to provide vaccine coverage with safe, effective vaccines that reach all children in the United States [2].

The year 2000 has been designated by the WHO as the target year for worldwide eradication of poliomyelitis [3•]. Substantial progress has been made toward that goal, with no cases of polio reported from the Americas since 1991, none from the Western Pacific region since March 1997, and none in the European region (except for Turkey) in 1998. Ongoing civil conflicts, however, particularly in Africa, and large reservoirs of cases such as that in the Indian subcontinent make the ultimate job of eradication difficult (Fig. 1). The global epidemiology of polio has implications for travelers who might be due for an adult booster against poliomyelitis if exposed during a trip. Given the current situation, travelers to the Indian subcontinent and Africa should be targeted. Of note, in an effort to eliminate cases of vaccine-associated paralytic poliomyelitis in the United States, the Advisory Committee on Immunization Practices (ACIP) has recommended that the entire primary series of vaccine be given with inactivated polio vaccine [4].

Despite the availability of a safe and effective measles vaccine, measles transmission, morbidity, and mortality remain high throughout the world except in the Americas and Western Pacific [5]. Continued support for vaccine programs by nongovernmental, public health, and national organizations will be critical in order to achieve control.

Table 1. Vaccines for travelers

Hepatitis A
Immune globulin
Inactivated
Hepatitis B
Influenza
Japanese encephalitis
Measles (mumps, rubella)
Neisseria meningitidis
Poliomyelitis
Oral, attenuated
Parenteral, inactivated
Rabies
Human diploid cell
Purified chick embryo cell
Rabies vaccine adsorbed
Salmonella typhi
Whole cell, inactivated
Oral, attenuated (Ty21a)
Vi polysaccharide
Streptococcus pneumoniae
Tetanus and diphtheria
Vibrio cholerae
Yellow fever

The success of smallpox eradication in the 1970s was revisited this year when world bodies considered the planned destruction of the two known stocks of variola virus held at the Centers for Diseases Control and Prevention (CDC) in the United States and the State Research Center of Virology and Biotechnology in Russia [6•]. These stocks were scheduled to be destroyed in June 1999, but destruction was delayed until 2002 following a May 1999 meeting of the World Health Assembly. The decision was ostensibly based on the scientific grounds of not wanting to permanently destroy the virus. Destruction would make the virus unavailable for study and therefore unable to provide important scientific and medical information for the development of vaccines and antivirals and for understanding pathogenesis. However, it seems that officials in many countries, including the United States, were concerned that in reality the virus was held in more than the two designated sites and could be used in terrorist attacks. A decision was made to form a committee to recommend research on variola and to devise a timetable for eventual destruction. It should be noted that the vaccine against smallpox uses the vaccinia virus and not the variola virus. Also, destruction of the virus would not eliminate genetic material because there are archival stocks of cloned DNA and γ-irradiated smallpox virus infected material at the US and Russian sites.

Vaccines Against Enteric Infections

Rotavirus

Rotavirus is the most common cause of severe diarrhea in children in the United States and is responsible for 30% to 50% of all hospitalizations for diarrhea in children younger than 5 years of age (approximately 50,000 per year) [7•]. Worldwide, rotavirus may cause 125 million cases of diarrhea annually and account for 25% of deaths due to diarrheal disease and 6% of all deaths in children younger than 5 years of age [8•]. In Lima, Peru, for example, rotavirus was detected in 52% of children hospitalized with diarrhea and was particularly associated with severe diarrhea (odds ratio, 2.3; 95% CI, 1.6 to 3.2) [9]. A live, oral attenuated vaccine introduced in the United States in 1998 has been added to the schedule for routine childhood immunization [2]. It is reviewed both in the statement by the ACIP in the United States [7•] and in a position paper from the WHO [8•], which is part of the new WHO series on vaccines.

The vaccine is a live, attenuated virus expressing four rotavirus serotypes. This is accomplished by having a rhesus monkey rotavirus of one serotype carry human rhesus gene reassortments for the other three serotypes. In trials in the United States, Finland, and Venezuela, three doses of the vaccine have demonstrated 49% to 68% efficacy in preventing infection and 69% to 91% efficacy in preventing severe diarrhea [7•]. Ideally, the vaccine should be given to infants at 2, 4, and 6 months of age; it can be administered safely with other childhood immunizations. For the United States, vaccination has been determined to be cost-effective from a societal perspective, but the cost of the vaccine would need to be lowered to $9 per dose for the health care system to break even [10]. The WHO has reserved judgment about inclusion of the vaccine in vaccine programs of developing nations until more studies have been carried out in developing world settings [8•].

In prelicensure studies, the vaccine was found to be well tolerated; the most common side effect was fever, which usually occurred 3 to 5 days after the first dose was given. Also seen were five cases (among 10,054 doses of vaccine) of intussusception, but this was not statistically more frequent than in placebo recipients. Following licensure in the United States, 15 cases of intussusception have been passively reported between September 1998 and the first week of July 1999 to the Vaccine Adverse Experience Reporting System (VAERS) [11]. Although this number may not be higher than expected (there is a normal frequency of about 50 cases per 100,000 infant-years), active surveillance for intussusception in California and Minnesota showed vaccine-associated frequency rates of 314 and 292 per 100,000 infant-years, respectively. Based on this preliminary analysis, the CDC has recommended that all children scheduled to receive vaccine should postpone receipt until additional information attempting to establish a causal relationship between vaccination and this complication can be analyzed. Before the results of the CDC analysis could be made available, however, in October the maker of the vaccine removed it from the market.

Typhoid fever

There are now three vaccines against typhoid fever: a whole-cell (WC) inactivated vaccine introduced in the 1950s; an oral

Table 2. Effect of universal childhood immunization in the United States on disease morbidity

	Baseline 20th century	1998 provisional	
Disease	**Annual cases, *n*[*]**	**Cases, *n***	**Decrease, %**
Smallpox	48,164[†]	0	100
Diphtheria	175,885	1	100[‡]
Pertussis	147,271	6279	95.7
Tetanus	1314[§]	34	97.4
Poliomyelitis	16,316	0[¶]	100
Measles	503,282	89	100[‡]
Mumps	152,209[**]	606	99.6
Rubella	47,745	345	99.3
Haemophilus influenzae type b	20,000[††]	54	99.7

[*]The average number of cases is usually taken from a 3- to 5-year period before vaccine development or licensure.
[†]Average number of reported cases from 1900 to 1904.
[‡]Rounded to the nearest tenth.
[§]Estimated number based on tetanus deaths from 1922 to 1926, assuming a case-fatality ratio of 90%.
[¶]Excludes one case of vaccine-associated poliomyelitis in 1998.
[**]Number of cases in 1968, the first year of reporting and 1 year after vaccine licensure.
[††]Estimated from population-based surveillance before vaccine licensure in 1985.
Adapted from the Centers for Disease Control and Prevention [1••].

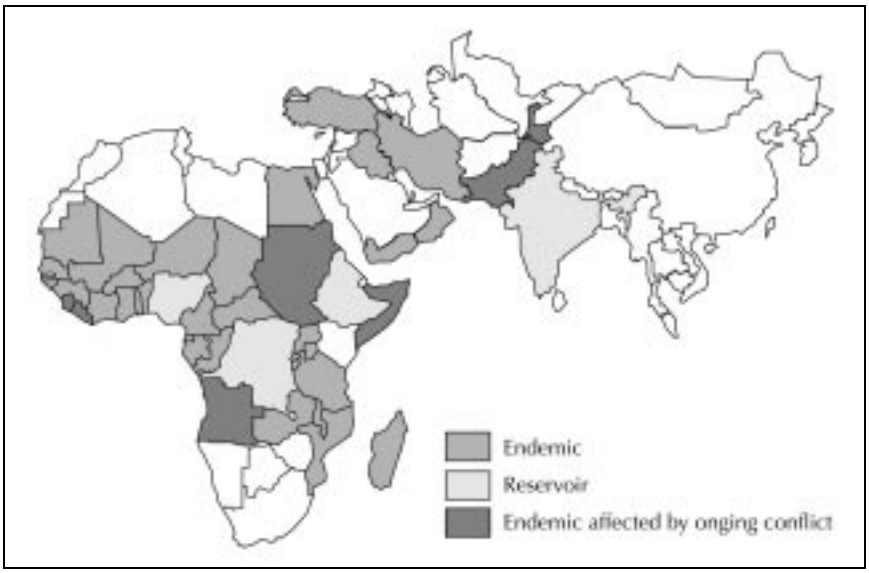

Figure 1. Global epidemiology of poliomyelitis for 1998. Countries in which poliomyelitis is endemic, countries considered to be a reservoir of poliovirus, and countries with ongoing armed conflict are indicated. (*From* the Centers for Disease Control and Prevention [3•].)

live, attenuated vaccine using the Ty21a strain of *Salmonella typhi* (Vivotif Berna) introduced in 1990; and a recently released (1996) capsular polysaccharide vaccine, Typhim Vi [12••]. The efficacy of these vaccines in nonimmune travelers has never been adequately tested beyond small challenge studies, so most information comes from field trials in developing world settings where there has probably been prior exposure to *S. typhi* in trial participants. Engles *et al.* [13••] published an important meta-analysis of 17 of these trials for which there was a control or placebo arm. Ten trials used the WC inactivated vaccine, five used the Ty21a oral vaccine, and two used the Vi antigen vaccine. Although these trials involved nearly 2 million participants, they were difficult to compare because of differences in the eras of study, trial participants, vaccine formulations, number of doses, and dosing intervals. No trials have directly compared vaccines.

The 3-year cumulative efficacy rates were 73% (95% CI, 65% to 80%) for two doses of WC vaccine, 51% (95% CI, 35% to 63%) for three doses of Ty21a vaccine, and 55% (95% CI, 30% to 71%) for the Vi antigen vaccine (only one study was analyzed) [12••]. In assessing toxicity, WC vaccines were associated with the most side effects, particularly fever (15%) and injection-site swelling (20%), with 10% of recipients missing school or work. The duration of efficacy was estimated to be 5 years for WC preparations, 4 years for Ty21a, and 2 years for the Vi antigen [12••]. It should be noted that the United States has adopted a four-dose schedule for Ty21a rather than the three-dose schedule studied in the reviewed trials because of improved efficacy with four doses.

The oral vaccine is well tolerated but requires patient compliance (*ie*, refrigeration of the vaccine and ingestion

Table 3. Number of typhoid fever cases reported in the United States and estimated rate per million travelers (1985–1994)*

Area visited	Total cases in US citizens, *n*	Cases per 10^6 US citizens, *n*	Total cases in non–US citizens, *n*	Cases per 10^6 non–US citizens, *n*
Mexico	204	1	140	2
Central America	34	5–6	64	16–21
South America	22	2	23	2
Caribbean	22	<1	27	2–3
Europe	7	<1	6	<1
Middle East	2	<1	3	1–2
Africa	10	4–14	13	9–28
Asia				
Indian subcontinent	182	110–410	212	161–1117
Southeast	127	5–12	87	9–12
Oceania	2	<1	4	<1

*Based on data for 1196 travelers for whom citizenship was known and who traveled to a single regional destination. Case rates were determined by using embarkation, debarkation, and in-flight survey data for the denominator.
Adapted from Mermin *et al.* [15•].

of four doses on alternate days). A compliance study by Cryz [14] at the Swiss Serum and Vaccine Institute (the vaccine manufacturer) indicated that most compliance errors were in taking the vaccine on alternate days (90% compliance). There was only a 70% response rate to the study survey, which could bias the results if noncomplaint individuals did not return the questionnaire. Importantly, the study also reported on the temperature stability of the Ty21a vaccine. At room temperature, vaccine potency was maintained for up to 7 days; at 30°C to 33°C, potency was maintained for 3 to 5 days.

In considering whether to vaccinate travelers against typhoid fever, it is helpful to know the risk. The CDC recently reviewed 2445 cases of typhoid fever in the United States from 1985 to 1994 [15•]. The findings were compared with an earlier review of cases from 1975 to 1984 [16]. From 1985 to 1994, 72% of typhoid cases were associated with travel compared with 62% in the earlier review. Six countries accounted for 80% of the cases: Mexico (28%), India (25%), the Philippines (10%), Pakistan (8%), El Salvador (5%), and Haiti (4%). The proportion of typhoid cases from Mexico decreased over the decade studied (46% to 23%), whereas the proportion increased from the Indian subcontinent (25% to 37%); the incidence was 18 times higher in those traveling to the Indian subcontinent than in travelers to any other destination. Only 3% of the 1305 patients who traveled and for whom a vaccination history was known had received a typhoid fever vaccine. Resistance to ampicillin, chloramphenicol, or trimethoprim-sulfamethoxazole increased in typhoid isolates. Isolates from 1990 to 1994 were more likely to be resistant to one or more of these antibiotics than were isolates from 1985 to 1989 (30% vs 12%). Thus, vaccination should be particularly targeted to travelers to the Indian subcontinent, as well as to those with more rural exposure to other regions of the developing world (Table 3). Because of increased resistance [17], it may be prudent for travelers to carry a quinolone antibiotic for self-treatment of diarrhea.

Cholera

There is continued interest in vaccination against cholera, although the WC inactivated, parenteral vaccine has limited efficacy and is poorly tolerated. Two oral vaccines have been widely studied: a WC vaccine with native or recombinant B-subunit of cholera toxin (BS-WC) and a live, attenuated vaccine of the CVD 103-HgR strain, which is commercially available in some countries outside the United States. Despite licensure of CVD 103-HgR in Canada, their Committee to Advise on Tropical Medicine and Travel has recommended vaccine only for such high-risk travelers as aide workers or health professionals working in endemic areas [18]. Their recommendation is based mostly on the extremely low risk (about one case per million North American travelers) of acquiring cholera for international travelers.

The use of cholera vaccine in refugee settings has received much interest following thousands of deaths from cholera in Rwandan refugee camps in 1994. Does vaccination play a role in preventing death from cholera in these settings? Thoughtful analysis of this issue has recently been published [19••, 20,21]. Provision for managing a cholera outbreak with rehydration therapy is the most cost-effective plan [19••]. Vaccinating refugees at the establishment of the camp is not cost-effective unless the cost of vaccine (BS-WC) were to fall below $0.22 per dose. Because of the time interval required for the vaccine to take effect, vaccination at the time of the outbreak would not confer protection unless the outbreak became sustained. Provision of potable water and proper disposal of sewage, with the capacity to treat diarrhea, is generally the best strategy to prevent and manage cholera and other dehydrating or severe diarrheal illness [20,21] .

Enterotoxigenic *Escherichia coli*

The oral recombinant BS-WC cholera vaccine was found to have modest protection against enterotoxigenic *Escherichia coli* (ETEC) [22,23], the most common cause of traveler's diarrhea. Using a similar concept, an oral ETEC vaccine has been developed. This vaccine consists of five formalin-killed ETEC isolates that have the major colonization factor antigens (CFAs) or their subcomponents (CFA/I, CFA/II, and CFA/IV) combined with the recombinant B subunit of the cholera toxin (ETEC/rCTB). In anticipation of carrying out efficacy trials in children in the developing world, two studies reviewed the safety and immunogenicity of this vaccine in Egyptian adults [24] and children [25•]. In the first study, 74 Egyptian adults received two doses of either vaccine or placebo at a 2-week interval [24]. The vaccine was added to 150 mL of sterile water to which was added a bicarbonate–citric acid buffer. Although there was a trend toward increased nausea and abdominal discomfort in those receiving the vaccine, this was not significant and affected less than 25% of vaccinated individuals. A mucosal immune response was measured by detecting IgA antibody secreting cells (ASCs) against rCTB and CFAs in the peripheral blood. After two doses of vaccine, over 90% of recipients responded to three of the five antigens tested, and most of those who responded did so after the first dose [24].

In the second study of two cohorts of Egyptian children (6 to 12 and 2 to 5 years of age) [25•], the vaccine was very well tolerated; more than 90% of children in both groups had no symptoms following vaccination. Immunogenicity was measured by IgA-ASC and by antibody itself. Over 92% of school-age children who received the vaccine had a twofold increase in ASCs to three of the four CFAs, and more than 80% of the preschool-age children responded to the two CFAs tested [25•]. More than 90% of the children in both groups had a fourfold or higher increase in IgA antibody to rCTB. One difficulty encountered in the study was in having the younger children drink the 50 mL of liquid required to ingest the vaccine; 13% of the doses were not ingested completely. Future efforts will need to be made to adjust the volume for infants and younger children.

Thus, the ETEC/rCTB vaccine was safe and immunogenic in endemically exposed populations of adults and children 2 to 12 years of age. This finding has led to as yet unpublished safety and immunogenicity studies in infants 6 to 18 months of age as well as to efficacy trials [26•]. Infants will receive a three-dose regimen because their anti-CFA antibody titer (a good marker for blood ASCs) was slightly lower on the two-dose schedule.

One unique approach to vaccination is to introduce vaccine genes into foodstuffs that will express the antigen. This approach was taken by the Center for Vaccine Development at the University of Maryland, which introduced into potatoes the B subunit of the heat labile enterotoxin (LT-B) of ETEC [27]. Fourteen adult volunteers ingested raw transgenic potatoes. Although some complained of nausea, they developed antitoxin-ASCs after each of three doses, and 10 of 11 developed a fourfold rise in IgG antibody against LT-B. Half of the volunteers also developed stool IgA.

New, safe vaccines against ETEC could be targeted against children and travelers [26•]. Although rotavirus more commonly causes dehydrating diarrhea, ETEC is the more common pathogen overall. It could be expected that a vaccine that combined the major CFAs and LT would prevent diarrhea in up to 20% of children and an even higher percentage in travelers.

Hepatitis A

The release in the United States of two inactivated vaccines against hepatitis A (Havrix [SmithKline Beecham] in 1995 and Vaqta [Merck] in 1996) has provided travelers and others with the option of long-term protection against the most common vaccine-preventable travel illness. Although the manufacturers recommend that vaccine be given at least 2 weeks before departure, this interval is not always possible. Is a shorter time interval sufficient to protect travelers? In the original trial of Vaqta in children, no cases of hepatitis A occurred after day 19 following vaccination [28], suggesting some protection after exposure.

Italian investigators examined the ability of Havrix to prevent secondary infection in household contacts of sporadic cases of hepatitis A [29•]. Persons in households with cases were given either Havrix or no vaccine within 8 days of diagnosis of the index case. Of the 75 households that did not receive vaccine, 10 (13%) reported cases of hepatitis A compared with only two of 71 households (2%) that received vaccine—for a protective efficacy of 79% [29•]. Overall, 12 cases occurred among 207 unvaccinated contacts and two cases occurred among 197 vaccinated contacts. These two cases were also asymptomatic, suggesting that vaccination mutes clinical illness. The authors conclude that vaccination after exposure is an acceptable way to control the spread of infection [29•]. The information from this study and the Vaqta trial [28] suggest that vaccination of travelers immediately before departure is likely to confer protection. This makes sense because the time for development of antibodies is about 2 weeks, and the average incubation period of hepatitis A infection is 28 days.

Vaccines Against Vector-Borne Infections

Yellow fever

Yellow fever has seen a resurgence throughout the endemic regions of the world (*ie*, equatorial regions of Africa and South America) [30]. In the past year in South America, increased yellow fever activity has occurred in the Para State of Brazil, and the first cases of urban yellow fever in South America in more than 40 years occurred in Santa Cruz, Bolivia [31•]. Outbreaks such as these may occur when a population is not immune to yellow fever and

there has been reinfestation of an urban area with the *Aedes aegypti* mosquito vector. Control of such outbreaks requires health care resources that are not always available. This increase in cases also places travelers in endemic regions at risk for infection [32]. With an excellent, effective, and longlasting vaccine there is no reason not to immunize travelers if they are at risk.

Few serious side effects have been reported for yellow fever vaccine, and anaphylaxis is considered extremely unusual. Kelso *et al*. [33] reviewed all reports of adverse reactions submitted to the VAERS in the United States between 1990 and 1997. Of the 40 reported cases, other vaccines had been administered simultaneously in 18. The rate of anaphylaxis, assuming that all cases were secondary to yellow fever vaccine, was 40 cases per 5,236,820 doses or about one in 131,000. In 34 of 35 cases, anaphylaxis followed the first administration of vaccine, suggesting that the reaction was to vaccine components rather than to viral proteins. For the 20 cases listed as probable anaphylactic reactions, 12 occurred within 30 minutes of vaccine receipt. Thus, persons should be screened for allergy to eggs, chicken, or gelatin—the most likely allergens.

Yellow fever vaccine may be given simultaneously with the Ty21a oral typhoid vaccine and with the live, attenuated CVD 103-HgR cholera vaccine without a decrement antibody titers to yellow fever virus [34]. Indeed, the antibody titers were higher when Ty21a was given, suggesting a potential adjuvant effect of the Ty21a vaccine.

Because yellow fever vaccine is a live, attenuated vaccine, it should be avoided during pregnancy, although studies have suggested that it is probably safe if given inadvertently. In a Brazilian study [35], a cohort of pregnant women was inadvertently vaccinated during an outbreak control effort. This case-control study examined spontaneous abortion in vaccinated versus nonvaccinated women. There was an increased risk for abortion of 2.29 (95% CI, 0.65 to 8.03) in vaccine recipients, but it was not statistically significant. Nevertheless, unless a woman is at high risk for exposure during travel, vaccination should be avoided during pregnancy [12••].

Japanese encephalitis

The current method for protecting travelers against Japanese encephalitis is to avoid culicine mosquitoes in endemic regions of Asia and to receive vaccine if traveling to or working in these areas for prolonged periods during transmission seasons (or for shorter times if there is intense exposure) [12••]. The risk is increased with travel to areas of rice and pig farming because rice fields may be a breeding ground for the mosquito vector and pigs (as well as some species of wild birds) are a common reservoir for the virus. Because of infrequent but potentially serious and often delayed hypersensitivity reactions to the current mouse brain—derived vaccine (occurring in about 0.6% of recipients), alternatives have been sought [36,37•]. The best studied alternative is a live, attenuated hamster kidney–derived vaccine that is currently distributed only in China [36].

Fatal reactions to vaccination are rare, but the occurrence of a hyperthermic fatality in a soldier reinforces the need for caution concerning vaccination [38]. In this case, a 21-year-old, mildly obese man received heat-phenol inactivated WC typhoid vaccine and the first dose of Japanese encephalitis vaccine; he was also taking pseudoephedrine for weight loss. He collapsed 75 minutes after vaccination while on a 3-mile run, was found to have a core temperature of 108°F, and was asystolic. There was no evidence of urticaria or swelling. It is likely that multiple potential factors contributed to this death, including the combined pyrogenic effects of the vaccines, pseudoephedrine, and exercise and the potential sympathomimetic effects of pseudoephedrine.

Lyme disease

Lyme disease, caused by *Ixodes* tick–transmitted *Borrelia burgdorferi*, is a common problem for residents of the northeast and upper midwest United States. A slightly different clinical illness occurs in Europe. Until this year, the only prevention of Lyme disease was to avoid the tick vector (*ie*, by wearing protective clothing, using N,N-diethylmethylbenzamide (DEET)-containing repellents, undergoing tick checks, and seeking prompt therapy at the sign of an erythema migrans rash). Two studies of a recombinant outer surface protein A (OspA) vaccine were published in 1998 [39•,40]. These studies form the basis for the FDA submission for vaccine licensure for SmithKline Beecham and Pasteur Mérieux Connaught. Only the SmithKline product (LYMErix) has been approved for use as of mid 1999. The vaccine stimulates development of anti-OspA antibodies in the human host that are ingested by the feeding tick during its blood meal. These antibodies inactivate *Borrelia* in the tick gut before they can be transmitted to humans. Because OspA is minimally expressed by *Borrelia* once it is in the human host, these antibodies would not be as effective after *Borrelia* has been transmitted.

In a study of nearly 11,000 subjects 15 to 70 years of age, half received vaccine at 0, 1, and 12 months and the other half received placebo [39•]. The initial two doses were given before the highest transmission season for Lyme disease (April to August), and the 12-month dose was given before the next year's transmission period. Following two doses of vaccine, there was 49% protective efficacy against clinically manifest disease and 83% efficacy against asymptomatic infection. After the third dose there was 76% protective efficacy against clinical illness and 100% efficacy against asymptomatic infection. The overall risk of acquiring Lyme disease in this high-risk population over 20 months was 1.5%. Based on antibody titers, the duration of protective efficacy is limited and annual booster doses may be required. The vaccine was well tolerated by most persons; local side effects occurred in about 25% and myalgias and arthralgias in 3% to 4%.

LYMErix is not expected to provide protection against European strains of *Borrelia* because these strains may vary in their expression of OspA proteins [41•]. Thus, travelers to endemic regions within the United States or residents of these areas who have extensive exposure to tick-infested woodlands or grassy areas can consider vaccination. The limited efficacy and likely need for frequent boosters, as well as alternative approaches to controlling Lyme infection, make routine use of the vaccine less appealing.

Tickborne encephalitis

Another tick-transmitted infection is tickborne encephalitis. An excellent review of all aspects of the disease has been published [42•]. This flavivirus infection has a tropism for the central nervous system and is endemic to rural forested or grassy farm areas of Central and Eastern Europe and Russia and extends to the far eastern coast of Russia and into northern China. The infection is transmitted by *Ixodes* ticks in the spring, summer, and early fall. Illness is occasionally acquired by ingestion of unpasteurized milk from infected goats, cows, or sheep. Although preventive vaccines are available, they are not licensed in the United States. Complete protection usually requires several doses over a year, so they are not practical for most travelers. Alternatively, accelerated schedules over about 3 weeks exist. For long-term expatriates living in endemic areas, vaccination can be considered once residence is established. Short-term travelers should exercise tick prevention measures and not ingest unpasteurized milk products.

Rabies Prevention

There is heightened awareness of rabies transmission in the United States because of its increasing prevalence in raccoons, skunks, foxes, coyotes, and bats. Most human case of rabies in the United States are associated with either domestic exposure to bats (which may frequently be unrecognized) or to dogs during travel outside the United States [43•]. In most developing countries, dogs remain unvaccinated and are the highest risk for transmission to humans. Travelers to rabies-endemic countries should take precautions to avoid contact with all dogs and other potentially rabid animals such as monkeys. A dog bite requires thorough cleansing of the wound, preferably with soap and water or other virucidal agent, and postexposure prophylaxis consisting of either human or equine rabies immune globulin (RIG) and one of several tissue culture–derived vaccines. The potentially toxic nerve cell vaccines should be avoided. Travelers who know that they may be exposed to animals on their trip or who would find it difficult to obtain safe postexposure treatment (PET) can consider preexposure vaccination [44••]. Rabies-free countries are listed in the CDC publication *Health Information for International Travel* [12••].

The currently licensed US vaccines are human diploid cell vaccine (HDCV), human rabies vaccine adsorbed, and purified chick embryo cell vaccine. Each vaccine is available for intramuscular pre- or postexposure dosing; only HDCV can be given intradermally for preexposure prevention. The receipt of preexposure vaccine makes it easier in the event of a rabies exposure: only two doses of vaccine are required and the need for RIG is eliminated. Preexposure vaccine may also protect against unrecognized exposure, particularly in children.

Several studies dealing with PET overseas are of particular interest to travelers who have not received preexposure vaccine. Analysis of PET in public hospitals in Thailand [45] and in a hospital in Karachi, Pakistan [46•] highlights several problems. In Thailand over 150,000 courses of PET are given annually. All nerve cell–derived vaccines have been eliminated so that only tissue cell vaccines are used. In the Thai study, all hospitals understood the importance of wound management, and all sites carried tissue culture vaccines [45]. However, 36% of hospitals did not have RIG and over half indicated that supply of this product was a problem. Additionally, 43% of Thai sites were not aware of new WHO guidelines that recommend infiltrating the bite wounds with RIG using the entire volume if possible and giving any remaining volume intramuscularly at a site different from vaccine [45].

In Pakistan, 143 persons who had sought medical help for PET were interviewed [46•]. Wounds were not properly cleaned in 69% of patients, all patients received a nerve cell–derived vaccine, and less than 3% received RIG [46•]. These two studies indicate that it may be difficult, at least in some areas of the world, to find appropriate PET.

The challenge of obtaining PET was detailed in the *New England Journal of Medicine* in a discussion of the death of a 32-year-old American who developed rabies following a dog bite in Nepal [47•]. She failed to obtain PET in Nepal, Thailand, and Australia. Had she received preexposure treatment or been instructed during her pretravel visit about how to appropriately access health care following the bite, her death could have been prevented. This is one of the most important aspects of pretravel care—to give travelers health care contacts should they require them during their trip. There are several ways to facilitate this: by providing travelers with the names and numbers of US embassies and consulates; by having them contact International Medical Assistance to Travelers (716-754-4883), which maintains a list of English-speaking physicians throughout the world; or by suggesting health insurance coverage through one of nearly two dozen commercial companies.

In general, preexposure rabies vaccination provides long-term protection. Rather than giving booster doses of vaccine at routine intervals, the CDC now recommends serologic testing at 6-month or longer intervals depending on the person's risk category [44••]. If the titer is not acceptable, a booster can be given. Many European countries use preexposure schedules that differ from those in the United States. A French study used either a two-dose (days 0 and 28) or three-dose (days 0,

7, and 28) intramuscular primary regimen with HDCV or purified Vero cell vaccine followed by a booster at 1 year [48]. Over 96% of those receiving three doses of either vaccine still had protective titers at 10 years. The two-dose regimen was significantly less protective, particularly in the Vero cell vaccine group. A titer of 30 IU/mL or higher following the 1-year booster predicted a protective titer at 10 years in 100% of vaccine recipients. The United States follows a standard three-dose intramuscular or intradermal (with HDCV) primary schedule but not a routine booster at 1 year.

Finally, a DNA vaccine encoding rabies virus protected eight cynomolgus monkeys following challenge with the same virus [49]. This raises the possibility of a future DNA rabies vaccine.

Conclusions

In the United States, the application of vaccination strategies has led to decreases of over 99% in diphtheria, poliomyelitis, measles, mumps, rubella, and *H. influenzae* type b infection. On a global basis, poliomyelitis has been eradicated from the Western hemisphere, and the incidence has declined markedly in Europe and the Western Pacific. However, ongoing civil conflict in Africa and large reservoirs of polio in the Indian subcontinent present obstacles to ultimate eradication. Rotavirus vaccine has been released in the United States and holds promise in preventing severe childhood diarrhea, but the complication of intussusception following vaccination must be evaluated before universal use is accepted. Lyme disease vaccine has also been released, but it has limited efficacy against clinical disease, is not effective against Lyme disease overseas, and may require frequent boosting. An oral ETEC vaccine combining rCTB with WCs that express colonization antigens holds promise for protecting travelers and children in developing countries. A meta-analysis of the efficacy of the current typhoid fever vaccines (WC inactivated, oral attenuated, and Vi polysaccharide) indicates that they are only partially effective (50% to 70%) in previously exposed hosts, but that they still should be considered for travelers to the highest risk areas of the Indian subcontinent, Africa, Central America, and Mexico. Vaccination against cholera remains unnecessary for most travelers because of extremely low risk and limited vaccine efficacy. Vaccination with inactivated vaccines may play a role in the control of hepatitis A outbreaks. Also, it is likely that administration of hepatitis A vaccine immediately before departure will confer protection for travelers. Ongoing yellow fever activity in South America and Africa emphasizes the importance of protection against this disease with a safe and effective vaccine. The incidence of rabies in humans is on the rise in the United States, often resulting from unrecognized exposure to rabid bats; rabies is a risk to travelers to developing countries primarily via dog bites. Preexposure prophylaxis with one of three tissue culture vaccines available in the United States should be considered if travelers will be at risk during their trip or have limited access to PET.

References and Recommended Reading

Recently published papers of particular interest have been highlighted as:

- • Of importance
- •• Of major importance

1.•• **Centers for Disease Control and Prevention: Impact of vaccines universally recommended for children—United States, 1990–1998.** *MMWR CDC Surveill Summ* 1999, **48:**243–248.

This report documents the dramatic decrease in vaccine-preventable disease from before the vaccine era to 1998. Eradication of smallpox and wild-type polio and decreases of more than 95% in diphtheria, tetanus, pertussis, measles, mumps, rubella, and *H. influenzae* type b virus are some of the achievements.

2. Centers for Disease Control and Prevention: **Recommended childhood immunization schedule—United States, 1999.** *MMWR CDC Surveill Summ* 1999, **48:**12–16.

3.• Centers for Disease Control and Prevention: **Progress toward global poliomyelitis eradication, 1997–1998.** *MMWR CDC Surveill Summ* 1999, **48:**416–421.

This report details the accomplishments of the global effort to eradicate polio by the year 2000. Civil conflict in Africa and large reservoirs of infection in the Indian subcontinent, where over 50% of the world's polio cases occur, present challenges to ultimate eradication.

4. Centers for Disease Control and Prevention: **Recommendations of the Advisory Committee on Immunization Practices: revised recommendations for routine poliomyelitis vaccination.** *MMWR CDC Surveill Summ* 1999, **48:**590

5. Centers for Disease Control and Prevention: **Progress toward global measles control and regional elimination, 1990–1997.** *MMWR CDC Surveill Summ* 1998, **47:**1049–1054.

6.• World Health Organization: **Smallpox eradication: destruction of variola virus stocks.** *Wkly Epidemiol Rec* 1999, 74:188–191.

This is an interesting review of the postponed destruction of variola virus that was to take place in the United States and Russia. Destruction was originally planned for 1993, then 1995, and finally June 30, 1999, but has been delayed until 2002. Concern about loss of the virus for scientific study and fears that countries other than the United States and Russia hold the virus have led to this latest delay.

7.• Centers for Disease Control and Prevention: **Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children: recommendations of the Advisory Committee on Immunization Practices (ACIP).** *MMWR CDC Surveill Summ* 1999, **48 (No. RR-2):**1–20.

These statements from the ACIP are the expert opinion on the rotavirus vaccine and form the basis for its administration in the United States.

8.• World Health Organization: **Rotavirus vaccines: WHO position paper.** *Wkly Epidemiol Rec* 1999, **74:**33–38.

The WHO has begun a series of position papers on vaccines that present the epidemiology of disease on a global basis, the status of vaccine development, and the role that vaccination will have in control of disease. Readers can access these series via the WHO's web site (www.who.org).

9. Cama RI, Parashar UD, Taylor DN, *et al.*: **Enteropathogens and other factors associated with severe disease in children with acute watery diarrhea in Lima, Peru.** *J Infect Dis* 1999, **179:**1139–1144.

10. Tucker AW, Haddix AC, Bresee JS, *et al.*: **Cost-effectiveness analysis of a rotavirus immunization program for the United States.** *JAMA* 1998, **279:**1371–1376.

11. Centers for Disease Control and Prevention: **Intussusception among recipients of rotavirus vaccine—United States, 1998–1999.** *MMWR CDC Surveill Summ* 1999, **48:**577–581.

12.•• Centers for Disease Control and Prevention: In *Health Information for International Travel, 1999–2000.* Atlanta: US Department of Health and Human Services; 1999.
This is the definitive resource for US health personnel in deciding about the prevention of illness in travelers. Newly updated, the publication provides information on vaccine safety, schedules, and indications; malaria and yellow fever epidemiology on a country-by-country basis; and a wealth of information on the prevention of other travel-related illness.

13.•• Engles EA, Falagas ME, Lau J, Bennish ML: **Typhoid fever vaccines: a meta-analysis of studies on efficacy and toxicity.** *BMJ* 1998, **316:**110–115.
This paper is the first effort in recent years to analyze the efficacy of the three typhoid fever vaccines—WC inactivated, oral attenuated, and Vi polysaccharide. Although vaccine efficacy appeared low (50%–70%), differences in patient populations, the eras of study, and the number of doses and schedule made direct comparisons difficult. Travelers should always exercise caution when eating and drinking in foreign countries, regardless of whether they have received vaccine.

14. Cryz SJ: **Patient compliance in the use of Vivotif Berna vaccine, typhoid vaccine, live oral Ty21a.** *J Travel Med* 1998, **5:**14–17.

15.• Mermin JH, Townes JM, Gerber M, *et al.*: **Typhoid fever in the United States, 1985–1994: changing risks of international travel and increasing antimicrobial resistance.** *Arch Intern Med* 1998, **158:**633–638.
This is an update of typhoid fever in the United States, with particular emphasis on imported cases, which now account for 72% of US typhoid cases.

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17. Rowe B, Ward LR, Threfall EJ: **Multidrug-resistant** *Salmonella typhi***: a worldwide epidemic.** *Clin Infect Dis* 1997, **24(suppl 1):**S106–S109.

18. Committee to Advise on Tropical Medicine and Travel (CATMAT): **Statement on oral cholera vaccine.** *Can Commun Dis Rep* 1998, **24:**1–4.

19.•• Naficy A, Rao MR, Paquet C, *et al.*: **Treatment and vaccination strategies to control cholera in sub-Saharan refugee settings: a cost-effectiveness analysis.** *JAMA* 1998, **279:**521–525.
Although cholera does not present a risk to most travelers, cholera resulting from crowded and unsanitary conditions in refugee camps can be devastating and account for thousands of deaths within weeks. The analysis provided by these authors provides the basis on which to make life-saving decisions in the event of an outbreak of diarrheal illness. Vaccination against cholera is not as effective as having in place a rehydration therapy protocol.

20. Murray J, McFarland DA, Waldman RJ: **Cost-effectiveness of oral cholera vaccine in a stable refugee population at risk for epidemic cholera and in a population with endemic cholera.** *Bull WHO* 1998, **76:**343–352.

21. Waldman RJ: **Cholera vaccination in refugee settings [editorial].** *JAMA* 1998, **279:**552–553.

22. Clemens JD, Sack DA, Harris JR, *et al.*: **Cross-protection by B subunit-whole cell cholera vaccine against diarrhea associated with heat-labile toxin-producing enterotoxigenic** *Escherichia coli***: results of a large-scale field trial.** *J Infect Dis* 1988, **158:**372–377.

23. Peltola H, Siitonen A, Kyrönseppä H, *et al.*: **Prevention of travellers' diarrhoea by oral B-subunit/whole-cell cholera vaccine.** *Lancet* 1991, **338:**1285–1289.

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25.• Savarino SJ, Hall ER, Bassily S, *et al.*: **Oral, inactivated, whole cell enterotoxigenic** *Escherichia coli* **plus cholera toxin B subunit vaccine: results of the initial evaluation in children.** *J Infect Dis* 1999, **179:**107–114.
This paper reports on the efforts to develop a vaccine against ETEC, the most common cause of traveler's diarrhea and of childhood diarrhea in the developing world. This oral vaccine consists of killed *E. coli* organisms that express colonization antigens combined with rCTB. Although not an efficacy trial, this study examined immunogenicity in 2- to 12-year-old children and paved the way for studies in infants and then efficacy trials.

26.• World Health Organization: **New frontiers in the development of vaccines against enterotoxinogenic (ETEC) and enterohaemorrhagic (EHEC)** *E. coli* **infections: Part 1.** *Wkly Epidemiol Rec* 1999, **74:**98–101.
This is an excellent review of the status of vaccination against diarrheagenic *E. coli*.

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29.• Sagliocca L, Amoroso P, Stroffolini T, *et al.*: **Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial.** *Lancet* 1999, **353:**1136–1139.
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31.• Van der Stuyft P, Gianella A, Pirard M, *et al.*: **Urbanisation of yellow fever in Santa Cruz, Bolivia.** *Lancet* 1999, **353:**1558–1562.
This study analyzes the introduction of yellow fever into an urban area of Brazil. Infestation of the city with the *A. aegypti* mosquito and low vaccination rates led to the outbreak. Ongoing public health efforts are needed to prevent this from happening in other areas of South America and Africa.

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This is an excellent summary of the epidemiology of Japanese encephalitis and the role of vaccination in controlling the infection. The paper also reviews the status of vaccines other than the mouse brain–derived vaccine (currently the only product available in the United States).

38. Franklin QJ: **Sudden death after typhoid and Japanese encephalitis vaccination in a young male taking pseudoephedrine.** *Mil Med* 1999, **164:**157–159.

39.• Steere AC, Sikand VK, Meurice F, *et al.*: **Vaccination against Lyme disease with recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant.** *N Engl J Med* 1998, **339:**209–215.

The development of a vaccine against Lyme disease is encouraging for prevention of this infection, which is common in the northeast and upper midwest United States. The vaccine uses recombinant OspA of *Borrelia*. It provides modest protection for individuals against clinical illness (49% efficacy in the first season and 76% in the second) and is even more effective against asymptomatic infection. However, the ultimate role will need to be decided because regular booster doses may be necessary.

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This is an excellent, balanced statement on the use of vaccine for the prevention of Lyme disease.

42.• Dumpis U, Crook D, Oksi J: **Tickborne encephalitis.** *Clin Infect Dis* 1999, **28:**882–890.

This is an excellent review of tick-borne encephalitis, an arthropod-transmitted viral infection. Although vaccination is not available in the United States, and a year is generally required for full immunization, the vaccine can be considered for long-term travelers and expatriates to endemic areas of central and eastern Europe and Russia.

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This paper reviews the epidemiology and clinical presentations of human rabies since 1980.

44.•• Centers for Disease Control and Prevention: **Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices (ACIP).** *MMWR CDC Surveill Summ* 1999, **48 (No. RR-1):**1–21.

This paper provides newly updated recommendations for pre- and postexposure prevention of rabies. Important changes include the availability of a third tissue culture vaccine (purified chick embryo cell), the use of serologic testing in deciding whether booster doses are needed, the importance of infiltrating bite wounds with the complete volume of RIG, and lowering the threshold of PET following exposure to a bat.

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