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Recommendations for the Prevention of Malaria Among Travelers*

SUMMARY

Recommendations for the prevention of malaria among travelers have been developed by CDC in consultation with the representatives from the Offices of Medical Services of the Department of State and the Peace Corps; the Division of Experimental Therapeutics of the Walter Reed Army Institute of Research; the Office of the Surgeon General, U.S. Army; the Office of the Surgeon General, U.S. Air Force; and the Bureau of Medicine and Surgery, U.S. Navy.

Resistance of **Plasmodium falciparum** *to chloroquine has spread to most areas with malaria. Alternative drugs to chloroquine are either associated with adverse reactions, are of limited efficacy, or require complex and detailed instructions for use that reduce compliance. These factors have contributed to a threefold increase in the number of reported* **P. falciparum** *infections among U.S. travelers to malarious areas since 1980.*

A new drug, mefloquine (Lariam®), is expected to be highly effective against both chloroquine resistant and Fansidar® -resistant **P. falciparum** *infections. Mefloquine is now recommended as the drug of choice for travelers at risk of infection with chloroquine-resistant* **P. falciparum**. *Alternative drugs for travelers who cannot take mefloquine include 1) doxycycline alone or 2) chloroquine alone, with Fansidar® available for standby treatment while medical care is sought for evaluation of febrile illness when travelers are in a malarious area. Prospective travelers and health-care providers are advised to call the CDC Malaria Hotline at (404) 332-4555 for detailed recommendations for the prevention of malaria.*

Introduction

These recommendations replace the guidelines for malaria prevention published in ***Health Information for International Travel 1989 (1)***. The new recommendations were developed by CDC in consultation with representatives from the Offices of Medical Services of the Department of State and the Peace Corps; the Division of Experimental Therapeutics of the Walter Reed Army Institute of Research; the Office of the Surgeon General, U.S. Army; the Office of the Surgeon General, U.S. Air Force; and the Bureau of Medicine and Surgery, U.S. Navy.

Malaria in humans is caused by one of four protozoan species of the genus ***Plasmodium: P. falciparum, P. vivax, P. ovale,*** and ***P. malariae.*** All are transmitted by the bite of an infected female Anopheles mosquito. Occasionally, transmission occurs by blood transfusion or congenitally from mother to fetus. The disease is characterized by fever and "flu-like" symptoms incuding chills, headache, myalgia, and malaise, which may occur at intervals. Malaria may be associated with anemia and jaundice, and ***P. falciparum*** infections may cause kidney failure, coma, and death.

Resistance of ***P. falciparum*** to chloroquine has spread to most areas with malaria. Alternative drugs to chloroquine are either associated with adverse reactions, are of limited efficacy, or require complex and detailed instructions for use that reduce compliance. As a result, increasing numbers of U.S. travelers to malarious areas are being infected with ***P. falciparum.***

A new drug, mefloquine (Larium®), is highly effective against both chioroquine-resistant and Fansidar®-resistant ***P. falciparum*** infections. Mefloquine has been approved by the Food & Drug Administration for use as an antimalarial agent. These revised recommendations incorporate mefloquine in the armamentarium for prophylaxis of malaria.

*Reprinted from MMWR 1990;39 (No.RR-3):1-10.

Risk of Acquiring Malaria

Malaria transmission occurs in large areas of Central and South America, Hispaniola, sub-Saharan Africa, the Indian Subcontinent, Southeast Asia, the Middle East, and Oceania. The estimated risk of acquiring malaria varies markedly from area to area. This variability is a function of the intensity of transmission in both urban and rural areas within the various regions, and it also depends on itinerary and time and type of travel. During 1980-1988, 1,534 cases of *P. falciparum* among U.S. civilians were reported to CDC. Of these, 1,222 (80%) were acquired in sub-Saharan Africa; 112 (7%), in Asia, 100 (7%), in the Caribbean and in South America, and 100 (7%), in other parts of the world. Of the 37 fatal infections, 27 were acquired in sub-Saharan Africa.

Thus, most imported malaria among U.S. travelers was acquired in sub-Saharan Africa, even though only an estimated 90,000 Americans travel to sub-Saharan Africa each year. In contrast, an estimated 900,000 Americans travel to malarious areas of Asia and South America each year. This disparity in the risk of acquiring malaria reflects the fact that travelers to Africa are at risk in most rural and many urban areas and, moreover, tend to spend considerable time, including evening and nighttime hours, in rural areas where malaria risk is highest. Most travelers to Asia and South America, however, spend most of their time in urban or resort areas where there is limited, if any, risk of exposure, and they travel to rural areas mainly during daytime hours when there is limited risk of infection.

Estimating the risk of infecton for different categories of travelers is difficult, even if persons travel or temporarily reside in the same general areas within a country. For example, tourists staying in air-conditioned hotels may be at lower risk than backpackers or adventure travelers. Similarly, longer-term residents living in screened and air-conditioned housing are less likely to be exposed than are missionaries or Peace Corps volunteers.

Drug Resistance

Resistance of *P. falciparum* to chloroquine has been confirmed or is probable in all countries with *P. falciparum* malaria except the Dominican Republic, Haiti, Central America west of the Panama Canal, the Middle East, and Egypt (Figure 1). In addition, resistance to both chloroquine and Fansidar® is widespread in Thailand, Burma, Cambodia, and the Amazon basin area of South America, and resistance has also been reported in sub-Saharan Africa.

General Advice for Travelers to Malaria-Endemic Areas

All travelers to malarious areas of the world are advised to use an appropriate drug regimen and personal protection measures to prevent malaria; however, travelers should be informed that regardless of methods employed, malaria still may be contracted. Malaria symptoms may develop as early as 8 days after initial exposure in a malaria endemic area and as late as several months after departure from a malarious area, after chemoprophylaxis has been terminated. Travelers should understand that malaria can be treated effectively early in the course of the disease, but delay of appropriate therapy can have serious or even fatal consequences. Individuals who have symptoms of malaria should seek prompt medical evaluation, including thick and thin malaria smears, ***as soon as possible.***

Personal Protection Measures

Because of the nocturnal feeding habits of Anopheles mosquitoes, malaria transmission occurs primarily between dusk and dawn. Travelers should take protective measures to reduce contact with mosquitoes especially during these hours. Such measures include remaining in well-screened areas, using mosquito nets when sleeping, and wearing clothes that cover most of the body. Additionally, travelers should purchase insect repellent before travel for use on exposed skin. The most effective repellents contain N,N diethylmetatoluamide (DEET), an ingredient in many commercially available insect repellents. The actual concentration of DEET varies among repellents, ranging up to 95%. Some persons exposed to DEET have had potentially serious toxic encephalopathy. The possibility of adverse reactions to DEET will be minimized if the following precautions are taken:

- Apply repellent sparingly only to exposed skin or clothing;
- Avoid applying high-concentration products to the skin, particularly of children;
- Do not inhale or ingest repellents or get them into the eyes;
- Avoid applying repellents to portions of children's hands that are likely to have contact with eyes or mouth;
- Never use repellents on wounds or irritated skin;
- Wash repellent-treated skin after coming indoors;
- And if a suspected reaction to insect repellent occurs, wash treated skin and seek medical attention *(2)*.

Travelers should also purchase a pyrethrum-containing flying-insect spray to use in living and sleeping areas during evening and nighttime hours.

Permethrin (Permanone®) may be sprayed on clothing for protection against mosquitoes.

Chemoprophylaxis

Several factors should be considered in the selection of an appropriate chemoprophylactic regimen before travel. The travel itinerary should be reviewed in detail and compared with the information on areas of risk within a given country (*1*, pp. 15-61) to determine whether the traveler will actually be at risk of acquiring malaria. Additional factors should be considered, including 1) whether the traveler will be at risk of acquiring chloroquine-resistant *P. falciparum* malaria, 2) whether the traveler has previously experienced an allergic or other reaction to the anti-malarial drug of choice, and 3) whether medical care will be readily accessible during travel.

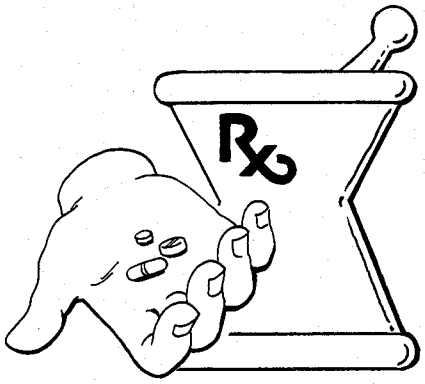
Malaria chemoprophylaxis should preferably begin 1-2 weeks before travel to malarious areas (except for doxycycline, which can begin 1-2 days before). In addition to assuring adequate blood levels of the drug, this regimen allows any potential side effects to be evaluated and treated by the traveler's physician. Chemoprophylaxis should continue during travel in the malarious areas and for four weeks after a person leaves the malarious areas (except for mefloquine, for which two tablets after the end of exposure are adequate; see below).

Chemoprophylactic Regimens

For travel to areas of risk where chloroquine-resistant *P. falciparum* has not been reported, once-weekly use of chloroquine alone is recommended. Chloroquine is usually well tolerated. The few people who experience uncomfortable side effects may tolerate the drug better by taking it with

meals or in divided, twice-weekly doses. As an alternative, the related compound hydroxychloroquine may be better tolerated. Chloroquine prophylaxis can begin 1-2 weeks before travel to malarious areas. It should be continued weekly during travel in malarious areas and for 4 weeks after a person leaves such areas. (See Table 1 for recommended dosages.)

For travel to areas of risk where chloroquine-resistant ***P. falciparum*** exists, use of mefloquine *alone* is recommended. The dose (250 mg for an adult) should be taken once each week for 4 weeks, followed by one dose every other week, as indicated in Figure 2. (See Table 1 for recommended dosages.) NOTE: In some foreign countries a fixed combination of mefloquine and Fansidar® is marketed under the name Fansimef®. Fansimef® should not be confused with mefloquine, and it is not recommended for prophylaxis of malaria.



Alternatives to mefloquine

Travelers to areas of risk where drug-resistant ***P. falciparum*** is endemic and for whom mefloquine is contraindicated may elect to use an alternative regimen, as follows:

Doxycycline alone taken daily is an alternative regimen for short-term travelers who are intolerant of mefloquine or for whom the drug is contraindicated. Travelers who use doxycycline should be cautioned about the possible side effects as described in the section on adverse reactions. Doxycycline prophylaxis can begin 1-2 days before travel to malarious areas. It should be continued daily during travel in the malarious areas and for 4 weeks after the traveler leaves the malarious area. (See Table 1 for recommended dosages.)

Chloroquine alone taken weekly is recommended for travelers who cannot use mefloquine or doxycycline, especially pregnant women and children under 15 kg. Travelers who elect to use chloroquine (except those with histories of sulfonamide intolerance) should be given a treatment dose of Fansidar® to be carried during travel. These travelers should take the Fansidar® promptly if they have a febrile illness during their travel and professional medical care is not readily available. They should be aware that this self-treatment of a possible malarial infection is *only a temporary measure and that prompt medical evaluation is imperative.* They should continue their weekly chloroquine prophylaxis after presumptive treatment with Fansidar®. (See Table 1 for recommended dosages for prophylaxis and Table 2 for presumptive treatment with Fansidar®.)

Mefloquine should not be used for self-treatment because of the frequency of side effects, especially dizziness, which has been associated with therapeutic dosages of mefloquine.

Proguanil is a dihydrofolate reductase (DHFR) inhibitor. Resistance of ***P. falciparum*** to DHFR inhibitors is present in many endemic regions, but its distribution is not well delineated. Proguanil (Paludrine®) is not available commercialy in the United States. Limited data suggest that it may be effective in East Africa but not Thailand, Pupua New Guinea, and West Africa. This lack of effectiveness may be due to drug resistance or to lack of compliance. If travelers use proguanil, it should be taken as a *daily* 200-mg dose (adult) in combination with *weekly* chloroquine.

Primaquine: prevention of relapses of *P. vivax* and *P. ovale*

P. vivax and ***P. ovale*** have forms that can persist in the liver and cause relapses for as long as 4 years after routine chemoprophylaxis is discontinued. Travelers to malarious areas should be alerted to this risk; if they develop malaria symptoms after they leave the malarious area, they should report their travel history and the possibility of malaria to a physician as soon as possible. Primaquine decreases the risk of relapses by acting against the liver stages of ***P. vivax*** and ***P. ovale;*** however, it is not indicated for all travelers. Primaquine is administered after the traveler has left an endemic area, usually during the last 2 weeks of the 4-week period of prophylaxis after exposure in an endemic area has ended.

Since most malarious areas of the world (except Haiti) have at least one species of relapsing malaria, travelers to these areas have some risk of acquiring either ***P. vivax*** or ***P. ovale.*** This risk, however, is extremely difficult to quantify. Prophylaxis with primaquine is generally indicated for persons who have had prolonged exposure in malaria-endemic areas, e.g., missionaries and Peace Corps volunteers. Although the actual risk to the traveler with less intense exposure is difficult to define, with the exception of individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) (see discussion of adverse reactions), most people can tolerate the standard regimen of primaquine. (See Table 1 for recommended dosages.)

Adverse Reactions and Contraindications to Antimalarials

The frequent or serious side effects of recommended antimalarials are discussed below. In addition, physicians should review the prescribing information in standard pharmaceutical reference texts and in the manufacturers' package inserts.

Chloroquine and ***hydroxychloroquine*** rarely cause serious adverse reactions when taken at prophylactic doses for malaria. Minor side effects may occur, such as gastrointestinal disturbance, headache, dizziness, blurred vision, and pruritus, but generally these effects do not require discontinuance of the drug. High dosages of chloroquine, such as those used to treat rheumatoid arthritis, have been associated with retinopathy, but this serious side effect has not been associated with routine weekly malaria prophylaxis. Nevertheless, periodic opthamologic examinations for persons using chloroquine for extended periods (more than 6 years of cumulative weekly prophylaxis) are recommended. Chloroquine and related compounds may exacerbate psoriasis. Chloroquine may interfere with the antibody response to human diploid cell rabies vaccine when it is administered intradermally.

Mefloquine has rarely been associated with serious adverse reactions (e.g., hallucinations, convulsions) at prophylactic dosage, but these reactions are more frequent with the higher dosages used in treatment. Minor side effects observed with prophylactic doses, such as gastrointestinal disturbance and dizziness, tend to be transient and self-limited.

Mefloquine is not recommended for use by travelers with a known hypersensitivity to mefloquine; children <15kg (30 lbs.); pregnant women; travelers using beta blockers or other drugs that may prolong or alter cardiac conduction; travelers involved in tasks requiring fine coordination and spatial discrimination, such as airline pilots; and travelers with a history of epilepsy or psychiatric disorder.

Extreme caution and close clinical monitoring is required when quinine is used to treat persons with malaria who have been

(Continued from page 3)
taking mefloquine prophylaxis, because quinine and mefloquine are similar regarding their pharmacology and cardiovascular and neurological toxicity.

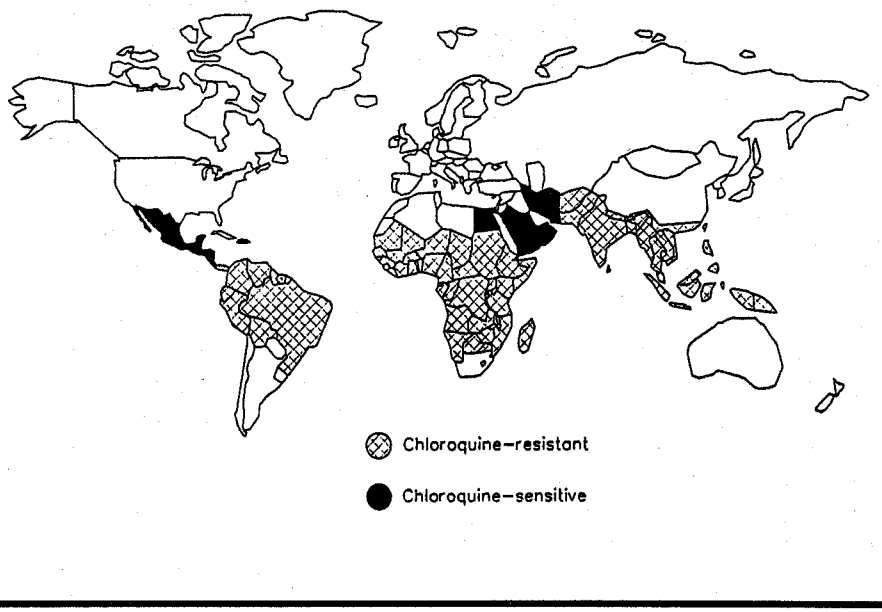
Mefloquine is a recently licensed drug in the United States, and experience with this drug -- when used for prophylaxis -- is limited. Some adverse reactions may not yet have been identified. Users of mefloquine who experience serious adverse reactions should consult their physicians, and the reactions should be reported to the Malaria Branch, CDC, telephone (404) 488-4046.

Doxycycline may cause photosensitivity, usually manifested as an exaggerated sunburn reaction. The risk of such a reaction can be minimized by avoiding prolonged, direct exposure to the sun; using sunscreens that absorb long-wave ultraviolet (UVA) radiation; and taking the drug in the evening. In addition, doxycycline use may be associated with an increased frequency of monilial vaginitis. Gastrointestinal side effects (nausea or vomiting) may be minimized by taking the drug with a meal. Tetracyclines are contraindicated for pregnant women and for children <8 years of age.

Proguanil rarely causes adverse reactions at prophylactic dosage. Reported side effects include nausea, vomiting, and mouth ulcers.

Primaquine may cause severe hemolysis in G6PD-deficient individuals. Before primaquine is used, G6PD deficiency should be ruled out by appropriate laboratory testing.

Figure 1. Malarious areas with **Plasmodium falciparum** resistant and sensitive to chlorine, 1990



Chemoprophylaxis for Children

Children of any age can contract malaria. Consequently, the indications for prophylaxis are identical to those described for adults. Mefloquine is not indicated for children <15 kg (30 lbs.) Doxycycline is contraindicated in children <8 years of age. (See recommended dosages in Table 1 and 2.)

Chloroquine phosphate is manufactured in the United States in tablet form only, and it tastes quite bitter. Pediatric doses should be calculated carefully according to body weight. Pharmacists can pulverize tablets and prepare gelatin capsules with calculated pediatric doses. Mixing the powder in food or drink may facilitate the weekly administration of chloroquine to children. Alternatively, chloroquine in suspension is widely available overseas. Parents should calculate the volume to be administered, because the concentration of chloroquine base varies in different suspensions.

Overdose of Antimalarial Drugs Can Be Fatal. The Medication Should Be Stored in Child-Proof Containers Out of Reach of Children.

Prophylaxis During Pregnancy

Malaria infection in pregnant women may be more severe than in nonpregnant women. In addition there may be increased risk of adverse pregnancy outcomes, including prematurity, abortion, and stillbirth. For these reasons, and because chloroquine has not been found to have any harmful effects on the fetus when used in the recommended doses for malaria prophylaxis, pregnancy is not a contraindication to malaria prophylaxis with chloroquine or hydroxychloroquine.

Women who are pregnant or likely to become so should avoid travel to areas with chloroquine-resistant ***P. falciparum*** because mefloquine and doxycycline should not be used during pregnancy. No alternative prophylactic regimen is completely effective in such areas.

Mefloquine should not be used during pregnancy. Women of childbearing potential who are taking mefloquine for malaria prophylaxis should take reliable contraceptive precautions for the duration of prophylaxis and for 2 months after the last dose of mefloquine.

Doxycycline is contraindicated for malaria prophylaxis during pregnancy. Adverse effects of tetracyclines on the fetus include discoloration and dysplasia of the teeth and inhibition of bone growth. In pregnancy, therefore, tetracyclines would be indicated only if required to treat life-threatening infections due to multi-drug resistant ***P. falciparum.***

Proguanil has been widely used for several decades, and no adverse effects on pregnancy or fetus have been established.

Primaquine should not be used during pregnancy because the drug may be passed transplacentally to a G6PD-deficient fetus and cause hemolytic anemia in utero. Whenever radical cure or terminal prophylaxis with primaquine is indicated during pregnancy, chloroquine should be given once a week until delivery, at which time the decision to give primaquine may be made.

Prophylaxis While Breast-Feeding

Very small amounts of antimalarial drugs are secreted in the breast milk of lactating women. The amount of drug transferred is not thought to be harmful to the nursing infant; however, more information is needed. Because the quantity of antimalarials in breast milk is insufficient to provide adequate protection against malaria, infants who require chemoprophylaxis should receive the recommended dosages of antimalarials (Table1).

Malaria Hotline

Detailed recommendations for the prevention of malaria may be obtained 24 hours a day by calling the CDC Malaria Hotline at (404) 332-4555.

Figure 2. Recommended doses of mefloquine for various lengths of stay in malarious areas

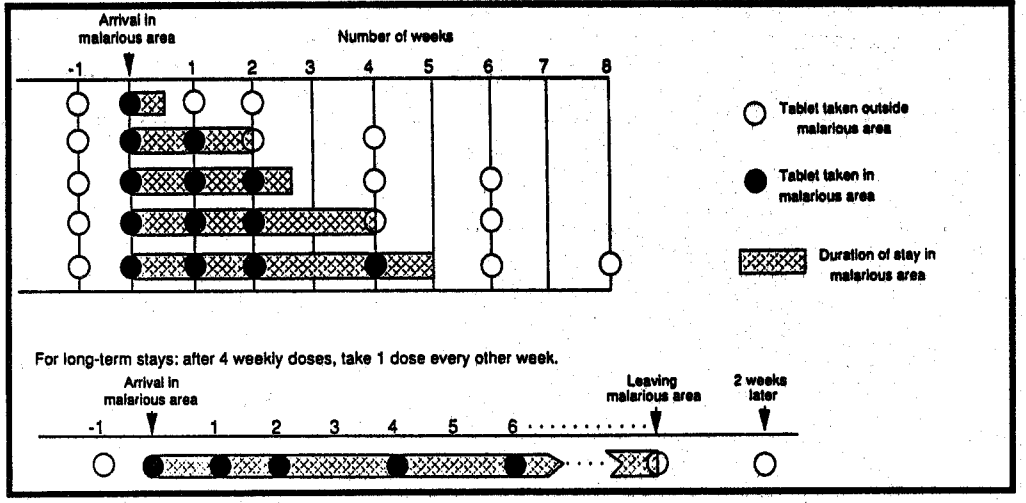


Table 1. Drugs used in the prophylaxis of malaria

Drug	Adult Dose	Pediatric Dose
Chloroquine phosphate (Aralen®)	300 mg base (500 mg salt) orally, once/week adult dose of 300 mg base	5 mg/kg base (8.3 mg/kg salt) orally once/week, up to maximum
Hydroxychloroquine sulfate (Plaquenil®)	310 mg base (400 mg salt) orally, once/week	5 mg/kg base (6.5 mg/kg salt) orally, once/week, up to maximum adult dose
Mefloquine (Lariam®)	228 mg base (250 mg salt) orally, once/week* 31-45 kg: 3/4 tab/wk* >45 kg: 1 tab/wk*	15-19 kg: 1/4 tab/wk* 20-30 kg: 1/2 tab/wk*
Doxycycline	100 mg orally, once/day 2 mg/kg of body weight orally/day up to adult dose of 100 mg/day	>8 years of age:
Proguanil once/day in combination with weekly chloroquine	200 mg orally, 2-6 years: 100 mg/day 7-10 years: 150 mg/day >10 years: 200 mg/day	<2 years: 50 mg/day
Primaquine orally, once/day for 14 days	15 mg base (26.3 mg salt) orally, once /day for 14 days	0.3 mg/kg base (0.5 mg/kg salt)

***The dose (250 mg for an adult) should be taken once each week for 4 weeks, followed by one dose every other week, as indicated in Figure 2.**

Table 2. Drug used in the presumptive treatment of malaria

Drug	Adult dose	Pediatric dose weight (kg):tablet(s)
Pyrimethamine-sulfadoxine (Fansidar®)	3 tablets (75 mg pyrimethamine and 1,500 mg sulfadoxine), orally as a single dose	5-10: 1/2 11-20: 1 21-30: 1 1/2 31-45: 2 >45: 3

Family Physicians & Pediatricians

Please note that section 32.1-46 of the Code of Virginia, Immunization of children against certain diseases, has been amended to include Hemophilus influenzae type b infections. Effective July 1, 1990, children must be immunized against Hemophilus influenzae type b "after ... the age of eighteen months and before ... the age of thirty months ..."

ANNOUNCEMENT

APIC-VA 16th Annual Educational Conference

Date: September 26-28, 1990

Place: Roanoke Airport Marriott
Roanoke, Va.

Theme: Moving Forward into the '90's

Contact: Martha Higgs, RN
(118)
VAMC
1970 Boulevard
Salem, Va. 24153

(703) 982-2463

References:

1. Centers of Disease Control. Health Information for international travel 1989. Atlanta: CDC, 1989; HHS pubication no. (CDC) 89-8280.
2. Centers of Disease Control. Seizures temporally associated with use of DEET insect repellent - New York and Connecticut. MMWR 1989;38:678-80.

Cases of notifiable diseases, Virginia, for the period May 1 through May 31,1990.

DISEASE	Total Cases Reported This Month						Total Cases Reported to Date		
		REGIONS					THIS YEAR	LAST YEAR	5 YR AVG.
	STATE	N.W.	N.	S.W.	C.	E.	(STATE TOTALS)		
Acquired Immunodeficiency Syndrome	54	6	10	1	13	24	259	170	104
Campylobacter Infections	33	8	9	4	10	2	174	205	175
Gonorrhea	1469	--	--	--	--	--	7341	6080	6457
Hepatitis A	31	0	2	12	5	12	115	128	111
B	15	0	3	5	3	4	93	117	164
Non A-Non B	3	0	1	2	0	0	15	24	28
Influenza	2	1	0	1	0	0	761	1774	2036
Kawasaki Syndrome	3	1	2	0	0	0	10	5	12
Legionellosis	0	0	0	0	0	0	6	2	5
Lyme Disease	9	0	0	0	1	8	18	5	5
Measles	23	3	19	0	0	1	50	11	36
Meningitis - Aseptic	8	2	4	0	1	1	70	63	59
Bacterial*	10	0	2	4	1	3	69	98	96
Meningococcal Infections	4	2	1	0	0	1	26	28	35
Mumps	29	18	10	1	0	0	58	47	43
Pertussis	1	0	1	0	0	0	9	4	13
Rabies in Animals	23	10	1	3	5	4	83	114	123
Reye Syndrome	1	1	0	0	0	0	1	1	1
Rocky Mountain Spotted Fever	2	1	1	0	0	0	2	0	2
Rubella	0	0	0	0	0	0	0	0	<1
Salmonellosis	92	13	15	11	18	35	384	365	435
Shigellosis	8	2	2	1	2	1	59	204	92
Syphilis (Primary & Secondary)	79	3	14	6	31	25	342	224	163
Tuberculosis	19	0	2	0	9	8	123	147	158

Localities Reporting Animal Rabies: Augusta 1 cat; Bath 1 raccoon; Clark 1 raccoon; Essex 1 raccoon; Frederick 1 skunk; Gloucester 1 raccoon; Highland 1 raccoon; Hopewell 2 raccoons; Loudoun 1 opposum; Newport News 1 raccoon; Northumberland 1 cat; Nottoway 1 raccoon; Page 2 skunks; Powhatan 1 fox; Prince George 1 raccoon; Pulaski 1 raccoon; Shenandoah 1 raccoon; Smyth 1 dog; Spotsylvania 1 raccoon; Warren 1 bat; Washington 1 skunk.

Occupational Illnesses: Asbestosis 7; Carpal Tunnel Syndrome 25; Coal Workers' Pneumoconiosis 41; Dermatitis 1; Loss of Hearing 10; Repetitive Motion Disorder 2.

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