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Summary of Antimalarial Drugs

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At least a dozen chemical compounds, commercially obtainable or under large-scale investigative use, are currently being recommended for the management of malaria. All of these, except quinacrine, pamaquine and the cinchona alkaloids, have been introduced during the past 5 to 10 years. Since the new drugs have appeared in medical literature under a variety of synonyms, including numbers and proprietary names, there is little wonder that much confusion prevails as to the identity and relative merits of the available antimalarial agents.

This summary is not intended to be a critical review of all recent advances in the chemotherapy of malaria. Original references should be consulted for detailed descriptions of the various drugs and for evidence to support the generalizations which are necessary in a summary. Those familiar with the problems of making definitive comparisons of therapeutically active compounds will appreciate the need for many qualifying statements throughout the appraisals. As the characteristics of the predominant strains of malarial parasites in a given area may greatly influence the choice of drug regimens, dosage recommendations are intended to be merely representative. In all cases they refer to the oral dosage for an average adult.

It is now accepted that the early development of sporozoite-induced malaria in man takes place in fixed-tissue cells, as has been demonstrated for *Plasmodium vivax* (*1*). It is further believed that persistent fixed-tissue forms, not yet actually demonstrated histologically, are responsible for the repeated relapses of *P. vivax* and *P. malariae* infections, but that such persistent forms do not occur in *P. falciparum* infections. In vivax and malariae malaria, drugs which are active only against the asexual erythrocytic parasites will stop acute attacks, or will suppress parasites and fever as long as administered, but will not prevent relapses. The actual relapse rates following

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such noncurative therapy will be determined by a variety of factors, including strain of parasite, intensity of exposure, and status of host resistance.

Curative chemotherapy of vivax or malariae malaria implies a significant reduction in the relapse rate, as contrasted with that following noncurative therapy, and presumably results from partial or complete destruction of persistent fixed-tissue parasites.

Protective treatment may achieve either causative prophylaxis or suppression. Causative prophylaxis implies action against the sporozoites or the succeeding pre-erythrocytic stages, prior to the first invasion of erythrocytes, and if complete, permanently prevents infection. Suppression implies action, usually against asexual erythrocytic parasites, sufficient to keep an infection latent at least as long as the drug is being administered. It may be carried out during a period of active exposure to infection, or it may follow treatment of an acute attack.

Gametocytocidal action indicates activity against the sexual erythrocytic parasites, which are necessary for the infection of mosquitoes. Such action, theoretically of public health value, does not in itself appear to affect the clinical course of malaria in the patient being treated.

All of the antimalarial drugs included in the summary are rapidly absorbed from the gastrointestinal tract. In the description of each drug a brief statement will be made as to its tissue localization, i. e., its tendency to become concentrated in certain cells of the body, and its rate of elimination, either by excretion or degradation. In general, a compound which is markedly localized in tissues is more effective if loading or priming doses are given at the start of therapy. Such a compound, particularly if its rate of elimination is slow, will be long retained in the body, permitting wider spacing of individual doses, shorter courses of treatment, and prolonged periods of protection against relapse immediately following therapy.

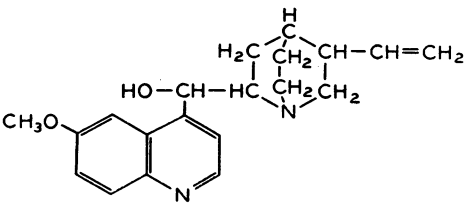
Names included in the U. S. Pharmacopoeia or approved by the Council on Pharmacy and Chemistry of the American Medical Association, will be used as principal designations. Official designations in other countries, code numbers, and proprietary names will be included as synonyms (without capitalization).

Data will be presented on the following:

Cinchona products: quinine, totaquine.
Acridine compounds: quinacrine.
4-aminoquinolines: chloroquine, oxychloroquine, sontochin, SN 10,751.
Biguanides: chlorguanide.
8-aminoquinolines: pamaquine, pentaquine, isopentaquine.

Quinine

6-methoxy-α-(5-vinyl-2-quinuclidyl)-4-quinolinemethanol



Salts: Sulfate of U. S. P. XIII (83 percent base) is the salt most commonly used in the United States; dihydrochloride (82 percent base) is the most soluble salt and is used parenterally. There are many other official and proprietary preparations.

Dosage:

Therapeutic: 2 grams per day (0.65 gram, or 10 grains, three times daily) for 7 days.

Suppressive: 0.65 gram (10 grains) per day.

Quinine is only slightly localized and is rapidly metabolized; plasma concentrations drop 90 percent within 24 hours after dosage (*2*).

The most important antimalarial action of quinine is against asexual erythrocytic parasites. This stops acute attacks, but clearance of parasites and subsidence of fever are often not as rapid as with large doses of quinacrine (*3*, *4*, *5*, *6*), or the better 4-aminoquinolines (*6*, *7*, *8*). Vivax malaria may relapse as early as one or two weeks after therapy (*6*, *9*, *10*). Quinine has limited effect upon vivax and malariae gametocytes but no effect on falciparum gametocytes (*11*, *12*).

Quinine has no causative prophylactic action. When given protectively, it will usually suppress *P. vivax* and *P. malariae*, but parasites appear after drug is discontinued. It is less efficient as a suppressant of *P. falciparum* (*13*).

Quinine is also important because of the potentiation observed when it is given in combination with certain 8–aminoquinoline drugs, resulting in lowered relapse rates in vivax malaria (*10*).

Quinine may be given intravenously, but should be given slowly in a large volume of fluid (*14*). It is not well absorbed from muscle and may cause local necrosis (*11*, *12*).

Therapeutic doses commonly cause cinchonism, with tinnitus, vertigo, partial deafness, visual disturbances, headache, and nausea. An occasional individual with idiosyncrasy may have severe cinchonism, urticaria or angioneurotic edema from a single small dose (*11*, *12*).

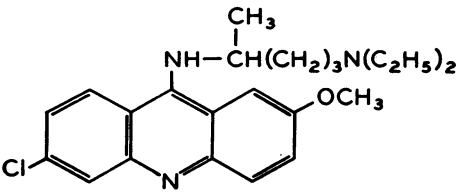
Totaquine

Totaquine is a standardized mixture of cinchona alkaloids, which according to U. S. P. XIII contains "not less than 10 percent of anhydrous quinine and not less than 70 percent and not more than 80 percent of total anhydrous crystallizable cinchona alkaloids, the remainder consisting substantially of diluents." A typical currently obtainable preparation contains 50 percent cinchonine, 18 percent cinchonidine, and 10 percent quinine. As all of these alkaloids possess antimalarial activity (*2*), treatment with totaquine results in more economical use of the active ingredients of cinchona bark.

Dosage is similar to that of quinine, and the therapeutic efficacy is essentially the same (*11*, *15*). It can only be given orally. Some preparations may produce nausea and vomiting more frequently than does quinine (*15*).

Quinacrine

6-chloro-2-methoxy-9(4-diethylamino-1-methylbutylamino)acridine



Synonyms: atabrine, atebrin, acriquine, chemiochin, chinacrin, crinodora, erion, haffkinine, italchina, mepacrine B. P., metoquina, metoquine.

Salts: hydrochloride of U. S. P. XIII is the dihydrochloride, dihydrate (79 percent base).

Dosage:

Therapeutic: 0.2 gram of salt x 5 (every 6 hours) on day 1; then 0.1 gram three times daily for 6 days, a total of 2.8 grams in 7 days.

Suppressive: 0.1 gram of salt per day.

Quinacrine is markedly localized, especially in leukocytes, liver, spleen, heart, and lungs (*16*, *17*). It is slowly eliminated, so that plasma concentrations drop only about 50 percent per week after the last dose (*18*).

The principal action of quinacrine is against asexual erythrocytic parasites. When loading doses are given, it stops acute attacks of malaria at least as rapidly as does quinine (*3*, *4*, *5*, *6*, *19*, *20*, *21*). Persistent exoerythrocytic stages of *P. vivax* are not affected; so vivax malaria will relapse, but parasites usually do not reappear until at least 4 to 6 weeks after treatment (*3*, *6*, *22*). Quinacrine resembles quinine in being ineffective against gametocytes of *P. falciparum* (*11*).

When given protectively, quinacrine has no causative prophylactic action, but it effectively suppresses erythrocytic parasites. Such

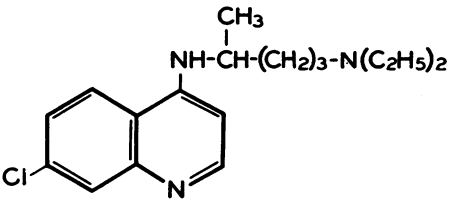
suppression, continued for a sufficient time after exposure (e. g., 4 weeks) permanently prevents falciparum malaria (*13*), although resistant strains have been demonstrated (*23*). Vivax (and probably malariae) infections appear after drug is discontinued (*13, 22, 24, 25*).

Quinacrine may be given intramuscularly in dosage of 0.4 gram (*16*). With rigid precautions it may be administered intravenously (*26*).

Although in recommended dosage quinacrine is usually well tolerated, more undesirable reactions occur than accompany treatment with 4–amino quinolines or (*26a*) chlorguanide. It temporarily dyes the skin yellow, but this is not a toxic reaction. It may produce anorexia, nausea, vomiting, and diarrhea, especially at the start of therapy. It is a cortical stimulant (*27*) and in susceptible subjects may cause temporary mental symptoms (*28*). In a small proportion of cases, serious skin reactions occur (*29*).

Chloroquine

7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline



Synonyms: aralen, resochin, nivaquine B, tanakán, SN 7618, 3377 RP.

Salts: diphosphate (62 percent base) for oral use; hydrochloride (89 percent base) for parenteral use. Nivaquine B is chloroquine sulfate.

Dosage:

Therapeutic: 1.0 gram of diphosphate (0.6 gram of base) as initial dose, followed in 6 hours by 0.5 gram (0.3 gram of base), then 0.5 gram (0.3 gram of base) once daily for 2 days, making a total of 2.5 grams of salt (1.5 grams of base) in 3 days.[1]

Suppressive: 0.5 gram of salt (0.3 gram of base) once weekly.

Chloroquine is markedly localized in liver, spleen, kidney, lungs, and white blood cells. Degradation and excretion are slow; plasma concentrations drop only about 60 percent per week after last dose (*30*).

The principal action of chloroquine is against asexual erythrocytic parasites (*31, 32*). It stops acute attacks of malaria promptly (*6, 7, 21, 30, 33, 34, 35, 35a*). It does not affect persistent exoerythrocytic stages, but vivax relapses are usually delayed until at least 7 to 10 weeks after treatment (*6, 7, 8, 35*). Falciparum infections are usually cured (*31, 32*). No data are available on quartan relapses. Gametocytes of *P. falciparum* resist chloroquine (*21, 34*).

[1] As with all slowly eliminated drugs, single-dose therapy (0.6 gram of base) will prove adequate in many cases, especially if followed by a suppressive course.

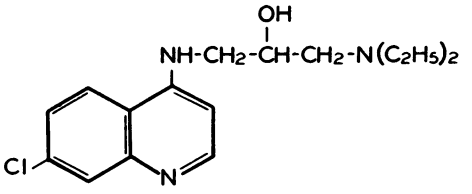
There is no action against pre-erythrocytic forms (*35*, *36*, *37*). Protective treatment suppresses parasites of all three species (*30*, *38*, *39*, *39a*, *40*, *41*, *42*, *42a*); *P. vivax* (and probably *P. malariae*) may appear after drug is stopped.

Chloroquine hydrochloride may be given intramuscularly in dosage of 0.2 to 0.3 gram of base (*43*). Very slow intravenous injection is still in an experimental stage (*44*).

Chloroquine produces few side-actions in recommended dosages (*26a*, *30*, *45*, *46*). It does not discolor the skin. Blurring of vision, pruritus, mild headache, and gastrointestinal complaints have been reported (*31*).

Oxychloroquine

7-chloro-4-(3-diethylamino-2-hydroxypropylamino)quinoline

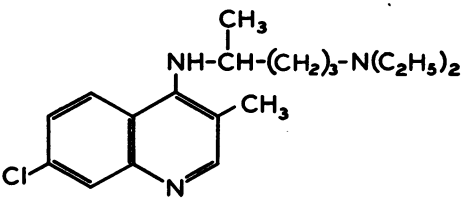


Synonym: SN 8137.
Salt: diphosphate (62 percent base).
Dosage: Not established.

Oxychloroquine, or SN 8137, resembles chloroquine in many respects. Although it is less toxic in man it is also slightly less active as an antimalarial (*30*). Small-scale trials in experimental and naturally-acquired malaria (*8*, *39*) have not shown any advantages over chloroquine. It has not been given definitive trial as a suppressant (*40*). Oxychloroquine is not commercially available.

Sontochin

7-chloro-4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline



Synonyms: SN 6911, 3038 RP, sontoquine, santoquine, santochin, nivaquine (except nivaquine B, which is a salt of chloroquine).
Salts: disulfate, monohydrate (61 percent base) has been most widely used in the United States. French investigators have used various other salts (*47*), of which nivaquine C, the dihydrochloride, is preferred.

Dosage:

Therapeutic: Dosages of base corresponding to those of chloroquine.

Suppressive: 0.1 gram of base per day; 0.3 gram twice weekly; or 0.3 gram once weekly (*48*).

Sontochin, like quinacrine and chloroquine, becomes concentrated in leukocytes, liver, spleen, and certain other body tissues; plasma concentrations decline about 25 percent per day after the last dose (*30*).

Like the other 4-aminoquinolines, sontochin acts against asexual erythrocytic parasites and alleviates acute attacks of malaria (*8, 30, 34, 47, 49, 50, 51*). Relapses of *P. vivax* can be expected at about the same intervals as after treatment with quinacrine (*51*), or sooner (*8*). It is not gametocytocidal against *P. falciparum* (*47, 50*).

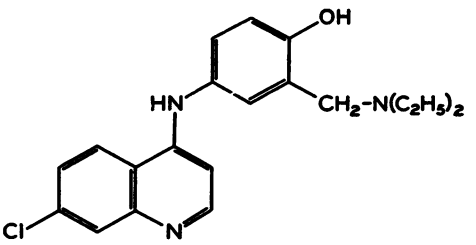
Sontochin is not a causative prophylactic (*36, 51*), but is an effective suppressant (*48, 51*).

Sontochin does not stain the skin and is well tolerated at recommended dosages (*52*). Parenteral use has been reported (*47*), but details are not available.

Sontochin is not commercially available in the United States.

SN 10,751

7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline



Synonyms: amodiaquin, camoquin, miaquin, CAM–AQ1.

Salt: dihydrochloride, dihydrate (77 percent base).

Dosage:

Therapeutic: Dosages of base corresponding to those of chloroquine.

Suppressive: Dosages of base corresponding to those of chloroquine; 0.6 gram of base every 2 weeks has also been provisionally suggested.

The drug is rapidly metabolized in the body. The degradation products are chemotherapeutically active and are slowly eliminated, plasma concentrations declining at the rate of about 60 percent per week *(53)*.

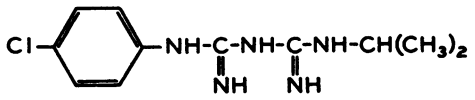
The antimalarial activity of this drug appears to be analogous to that of chloroquine *(21, 53, 54, 55)*. In controlled studies, relapses of vivax malaria are delayed after SN 10,751 almost as long as after chloroquine *(54)*. Falciparum infections are apparently cured.

In practical application, SN 10,751 has been shown to be well tolerated *(55, 56, 57)*. Lassitude, anorexia, and insomnia have been described with long-continued *high daily* dosage *(30)*.

This drug is not commercially available in the United States.

Chlorguanide

N_1-(p-chlorophenyl)-N_5-isopropyl biguanide



Synonyms: paludrine, proguanil B. P., M. 4888, guanatol, drinupal, palusil, tirian.

Salt: monohydrochloride (87 percent base) is commonly given orally. The acetate and lactate are more soluble and are recommended for parenteral use.

Dosage:

Therapeutic: 0.6 gram of hydrochloride per day (0.3 gram twice daily) for 10 days; alternative regimen (for *P. vivax* only), single dose of 0.3 gram, followed by suppressive course.

Suppressive: 0.3 gram of salt once weekly; 0.2 gram twice weekly; or 0.1 gram daily.

There is considerable localization of chlorguanide in erythrocytes, leucocytes, kidney, and liver *(58, 59)*. Chlorguanide as such disappears rapidly from the blood plasma after dosage, but there is evidence that at least part of it is converted into an active metabolic product *(60)*.

In *P. falciparum* infections, chlorguanide acts as a causative prophylactic *(61, 62)* and usually cures *(61, 63)*. Some strains of *P. falciparum* show resistance to the drug *(21, 62, 64, 65, 66, 67)* to a degree which has prompted the suggestion *(62)* that a more rapidly effective drug such as quinacrine be used for first day of treatment and that 0.1 gram of chlorguanide be taken daily for 6 weeks after therapy. Chlorguanide is an effective suppressant of *P. vivax* *(39, 41, 42a, 61, 63, 64)* and there is evidence of action against pre-erythrocytic stages *(61)*. All parasites are not eradicated, so that infections appear after suppression is discontinued. It alleviates acute attacks of vivax malaria over a wide dosage range *(34, 61, 65, 68, 69, 70)* but this effect is often relatively slow. Relapses of *P. vivax* occur at about the same rate and time as after quinacrine *(61, 68, 69, 70, 71, 72, 73)*. Chlorguanide stops acute attacks of quartan malaria *(61, 64)*; no data are available on prophylaxis or cure. Chlorguanide renders falciparum gametocytes noninfective to mosquitoes *(61, 62)*.

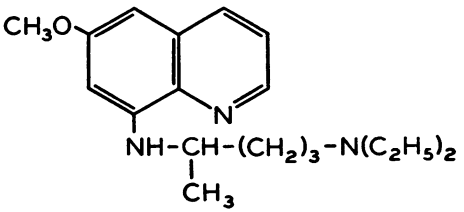
Acquired resistance to chlorguanide has been conclusively demonstrated in the malarias of lower animals *(74, 75, 76, 77)* and will soon be reported for human malaria *(67, 77a)*.

Chlorguanide acetate has been given intravenously in doses up to 100 mg. (*59*) or 400 mg., (*78*). Intramuscular injection has also been reported as well tolerated (*59*), although studies in lower animals provide evidence of local tissue damage (*79*).

The toxicity of chlorguanide is low. Dosages of 1.0 to 1.4 gram per day have been tolerated for 14 to 28 days without permanent ill-effects (*61*, *68*). With such high dosages, nausea, vomiting, diarrhea, and mild hematuria have been described (*61*).

Pamaquine

6-methoxy-8-(4-diethylamino-1-methylbutylamino) quinoline



Synonyms: plasmochin, plasmoquine, praequine, gamefar, quipenyl.

Salts: naphthoate (approximately 45 percent base), monohydrochloride (90 percent base).

Dosage:

Therapeutic: 30 mg. of base per day (10 mg. three times daily) concurrent with quinine sulfate, 2 grams per day (0.65 gram three times daily) for 14 days.

Suppressive: Not used.

Pamaquine is localized only to a moderate degree in liver, lungs, and brain, and it is quickly metabolized (*80*). Its physiological disposition is markedly altered by concurrent quinacrine or chlorguanide, leading to much higher plasma concentrations than with corresponding doses of pamaquine alone.

Pamaquine has relatively weak action on asexual erythrocytic parasites (*10*, *36*). Its practical usefulness results from the fact that it will destroy the persistent forms responsible for vivax relapses, an effect which is enhanced by the concurrent administration of quinine (*10*). Dosage of the order recommended above reduces relapse rates of naturally acquired vivax malaria (*81*, *82*, *83*, *84*, *85*, *86*, *87*, *88*) but will not cure early heavy infections (*10*, *89*).

In toxic dosage pamaquine will destroy the pre-erythrocytic forms of *P. vivax* and *P. falciparum* (*36*, *90*, *91*, *92*) but this action is only of theoretical interest, as an effective dosage cannot be long tolerated.

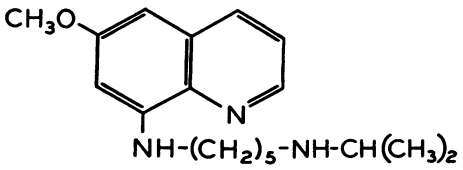
Small doses of pamaquine (e. g., 10 mg. three times daily for 5 days) will eliminate gametocytes of *P. falciparum*.

Pamaquine regularly produces methemoglobinemia (*93*) which, if of

sufficient degree (5 to 10 percent of total hemoglobin), will be accompanied by cyanosis; abdominal cramps are common. Acute intravascular hemolysis is an infrequent but serious reaction (*93*, *94*), more common in Negroes. Concurrent quinacrine or sulfonamides should be avoided with all 8-aminoquinolines (*95*).

Pentaquine

6-methoxy-8-(5-isopropylaminoamylamino) quinoline



Synonyms: SN 13,276.
Salt: phosphate (75 percent base).
Dosage:
Therapeutic: 60 mg. of base per day (10 mg. every 4 hours) or 30 mg. of base per day (10 mg. every 8 hours), given concurrently with quinine sulfate 2 grams per day (0.65 gram three times daily), for 14 days.
Suppressive: Not used.

Like pamaquine, pentaquine is rapidly degraded in the body (*96*). There is apparently only slight tissue localization. Concurrent quinine results in slightly higher plasma levels, but concurrent quinacrine produces greatly elevated plasma concentrations of pentaquine (*95*).

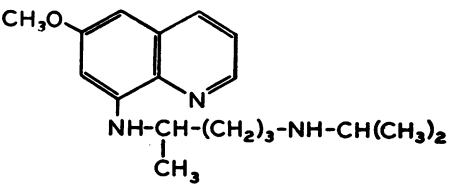
Although pentaquine has activity against the asexual erythocytic parasites of *P. vivax* (*97*, *98*), its real usefulness depends upon its ability, especially when given in combination with quinine, to lower the relapse rate of vivax malaria (*96*, *97*). The higher dosage given above is necessary for cure of heavy early experimental infections (*97*) but the lower dosage has lowered relapse rates of late, naturally acquired infections (*99*, *100*). The optimal dosage of concurrent quinine is not yet defined (*97*, *98*).

In very high dosage, pentaquine is a causative prophylactic against *P. vivax* (*92*), but its unsuitability for prolonged administration precludes such use in the field.

Pentaquine will produce a moderate elevation in methemoglobin, roughly proportional to dosage, so that some patients will exhibit cyanosis. Abdominal cramps, anorexia, nausea, vomiting, or drug fever may occur (*97*, *98*). Acute intravascular hemolysis is a potential hazard. Patients on the higher dosage should be hospitalized; those on the lower dosage may be ambulatory, but should be closely observed (*100*).

Isopentaquine

6-methoxy-8-(4-isopropylamino-1-methylbutylamino)-quinoline



Synonyms: SN 13,274.
Salt: mono-oxalate (74–79 percent base).
Dosage:
Therapeutic: Same as that of pentaquine.
Suppressive: Not used.

Isopentaquine is a close analogue of pentaquine. When given concurrently with quinine it is equal to pentaquine in reducing the relapse rate of experimental vivax infections and is somewhat less toxic (*101*). It is not commercially available.

Conclusions

Most of the newer compounds have not been studied under sufficiently varied conditions to warrant final conclusions as to their relative merits, but several of them appear to be superior to either quinacrine or quinine. The data at hand permit the following conclusions:

1. *Treatment of acute attacks of malaria.* Quinine, quinacrine, chloroquine (and analogous 4-aminoquinolines) and chlorguanide, when given in adequate dosage, will nearly always stop acute attacks of malaria. Choice of drug, therefore, depends upon such factors as rapidity of effect, incidence of side-actions, length of treatment period, incidence of falciparum relapses, latent periods before vivax relapses, natural or acquired strain-resistance, and the cost and availability of drug. Chloroquine is superior in most of these respects and is currently regarded as the drug of choice for routine therapy.

2. *Suppression of malaria.* The aforementioned drugs, when given in properly spaced doses, will usually keep malaria latent under conditions of exposure in the field or following therapy of an acute attack. Choice of drug depends upon the incidence of break-throughs and of undesirable side-actions, the required frequency of dosage, and the persistence of protection if doses are missed, as well as upon cost and availability. Chloroquine in weekly dosage has proved to be a satisfactory suppressant, but further comparative trials are needed to determine the relative merits of chloroquine, chlorguanide, and the less well known 4-aminoquinolines.

3. *Cure of vivax malaria.* In relapsing vivax malaria, concurrent treatment with quinine and an 8-aminoquinoline, such as pamaquine, pentaquine, or isopentaquine, offers the best chance of radical cure. Pentaquine and isopentaquine afford greater margins of safety between effective and toxic dosages.

ACKNOWLEDGMENT

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Prevalence of Poliomyelitis in 1948

By C. C. DAUER, M. D.*

Prevalence in the United States. Following a year during which the incidence of poliomyelitis was relatively low in the United States, the disease again occurred in widespread epidemic form in 1948.[1] A total of 27,680 cases was reported in 1948, about 2,000 more than was reported in 1946 (table 1), but less than the 29,061 cases reported in 1916 to the Public Health Service by 44 States and the District of Columbia.

Table 1. *Number of poliomyelitis cases and deaths, case and death rates per 100,000 population, and number of cases reported per death in the United States, 1943–48*

Year	Total cases reported	Total deaths registered [1]	Case rate	Death rate	Cases reported per death
1943	12, 449	1, 151	9. 3	0. 8	11. 1
1944	19, 029	1, 361	14. 3	1. 1	13. 3
1945	13, 619	1, 186	10. 3	. 9	11. 4
1946	25, 191	1, 845	18. 0	1. 3	13. 6
1947	10, 734	580	7. 4	. 4	18. 4
1948	27, 680	[2] 2, 140	18. 9	1. 5	13. 0

[1] From reports of the National Office of Vital Statistics.
[2] Based on 10-percent sample by National Office of Vital Statistics.

The morbidity rate in 1916 was 30.2 for this group of States, but only 18.9 for the country as a whole in 1948. Although no final figures are available at the time of writing this report on the number of deaths from poliomyelitis in 1948 for the entire country, a 10-percent sample indicates that the figure will be approximately 2,140, or a death rate of about 1.5 per 100,000 population.

The most extensive epidemic area in 1948 was in the west North Central part of the country (fig. 1), centering in South Dakota but also involving adjacent parts of Minnesota, Iowa, and Nebraska. An epidemic area of lesser extent, and with lower incidence rates (as will be indicated later), was located in North Carolina and a few adjacent counties in South Carolina, Tennessee, and Virginia. Still other epidemic areas were located in New Jersey and Delaware, in Ohio, various parts of Texas, the southern half of California, and Utah.

While California reported the largest number of cases (table 2), its morbidity rate was third highest for the States. On the other

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[1] All morbidity and mortality data for 1948 are provisional. The number of cases and deaths by States was obtained through the courtesy of the various State Departments of Health. Morbidity rates for States were based on provisional estimates of population for July 1, 1948, supplied by the Bureau of the Census. Morbidity rates by counties were based on estimates of population for November 1943, supplied by the Bureau of the Census with the exception of California, which was obtained from a publication by Heller, Brace and Company, New York, N. Y.

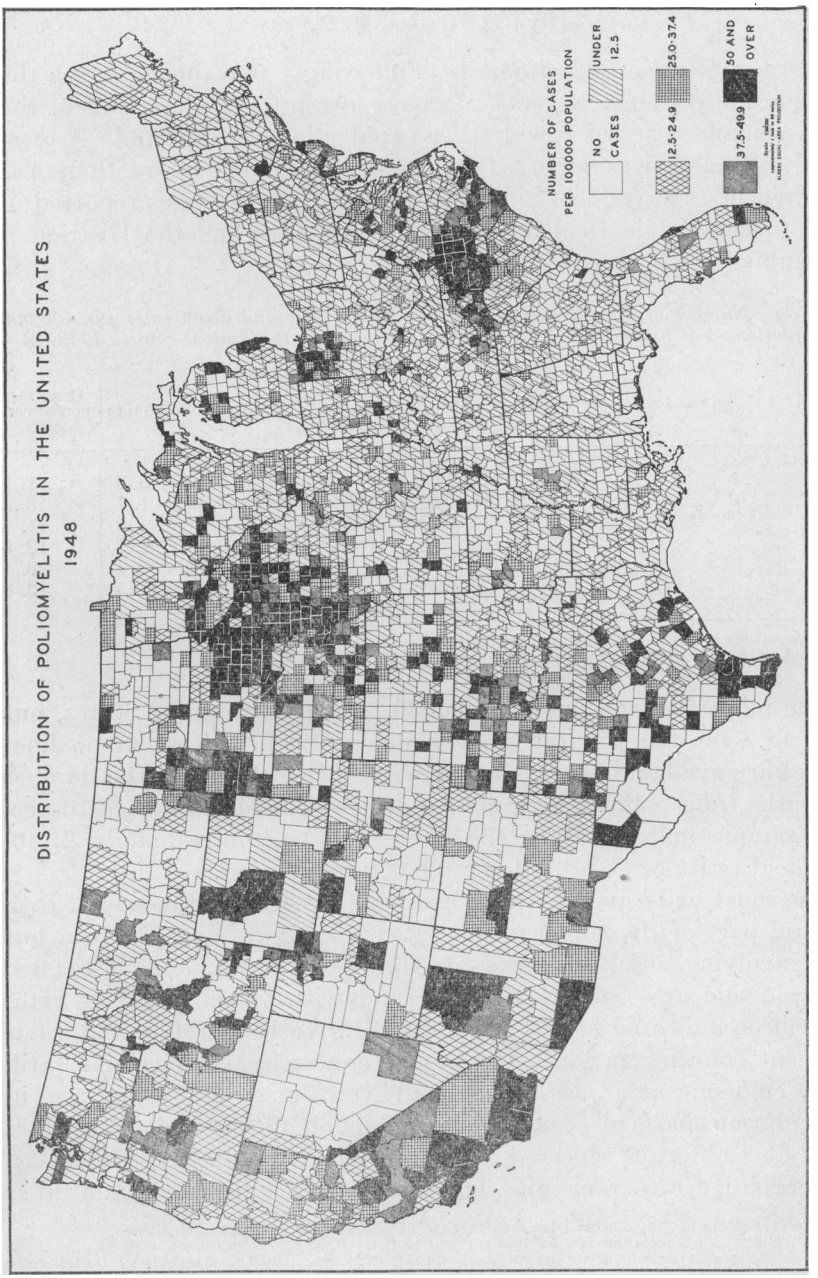
DISTRIBUTION OF POLIOMYELITIS IN THE UNITED STATES
1948
NUMBER OF CASES PER 100000 POPULATION
NO CASES
UNDER 12.5
12.5-24.9
25.0-37.4
37.5-499
50 AND OVER

Figure 1

Table 2. ***Number of poliomyelitis cases and deaths reported, case rates per 100,000 population, ratio of cases to deaths, and percent of nonparalytic cases, by States for 1948***

	Number cases	Number deaths	Case rate	Ratio cases to deaths	Percent of cases non-paralytic
New England:					
Maine	40	2	4.4	20.0	27.5
New Hampshire	24	1	4.4	24.0	25.0
Vermont	26	2	6.9	13.0	19.2
Massachusetts	175	----	3.7	----	65.7
Rhode Island	8	0	1.1	No deaths	37.5
Connecticut	121	0	6.0	No deaths	29.0
Middle Atlantic:					
New York	1,399	[1] 23	9.7	[1] 29.2	----
New Jersey	809	42	16.9	19.2	----
Pennsylvania	801	42	7.5	19.0	35.8
East North Central:					
Ohio	1,168	----	15.0	----	----
Indiana	385	29	9.8	13.3	24.7
Illinois	1,103	[2] 57	12.7	[2] 13.8	[2] 55.9
Michigan	770	55	12.4	14.0	44.3
Wisconsin	606	91	18.3	6.6	31.7
West North Central:					
Minnesota	1,378	98	47.0	14.1	48.0
Iowa	1,260	78	48.0	16.1	----
Missouri	319	33	8.1	9.7	----
North Dakota	130	7	13.2	18.5	----
South Dakota	890	101	142.8	8.8	----
Nebraska	717	30	55.1	23.9	----
Kansas	317	26	16.1	12.2	----
South Atlantic:					
Delaware	128	4	43.1	32.0	50.0
Maryland	171	10	8.0	17.1	19.9
District of Columbia	136	3	15.1	45.3	57.8
Virginia	568	26	18.8	21.8	72.5
West Virginia	179	----	9.3	----	----
North Carolina	2,506	147	67.4	17.0	----
South Carolina	378	16	19.0	23.6	15.0
Georgia	225	7	7.2	32.1	9.8
Florida	285	18	16.3	16.0	----
East South Central:					
Kentucky	201	9	7.1	22.3	16.4
Tennessee	376	----	11.9	----	0
Alabama	206	----	7.2	----	18.0
Mississippi	162	----	7.7	----	----
West South Central:					
Arkansas	146	----	7.6	----	10.0
Louisiana	169	17	6.5	9.9	8.8
Oklahoma	363	33	15.3	11.0	----
Texas	1,765	186	24.4	9.5	----
Mountain:					
Montana	65	8	12.9	8.1	26.1
Idaho	122	5	23.0	24.4	----
Wyoming	82	9	29.8	9.1	26.8
Colorado	125	10	10.7	12.5	0
New Mexico	79	7	13.8	11.3	20.9
Arizona	173	17	26.0	10.2	----
Utah	205	9	32.3	22.8	----
Nevada	19	1	13.4	19.0	----
Pacific:					
Washington	385	35	15.5	11.0	34.3
Oregon	218	12	13.4	18.1	----
California	5,796	----	57.7	----	----

---- Leaders indicate no data available.
[1] Exclusive of New York City.
[2] Exclusive of Chicago.

hand, South Dakota was ninth in number of cases reported but had the highest morbidity rate, more than double that of any other State.

The reported incidence in certain counties of South Dakota, Iowa, and Nebraska was excessively high. Eight counties in eastern South Dakota, having an aggregate estimated population of 115,000, re-

ported 563 cases or a rate of 490 per 100,000 population. The rates varied in these counties from 333 to 1,090. Beadle County, which had the highest rate in this group, has an estimated population of 16,641 (1943) and reported 181 cases or an attack rate of more than 1 percent. In Harrison County, Iowa, where an epidemic began before the closing of school in May, 93 cases were reported, a rate of 477. The nearest approach to morbidity rates of such order in other epidemic areas was Kimble County in Texas with a rate of 378. In North Carolina and California the maximum rates reported were 270 in Burke County in the former, and 120 in Kern County in the latter.

Seasonal occurrence of poliomyelitis. In 1948, as in previous years, there were striking differences in the seasonal occurrence of poliomyelitis in different parts of the country (fig. 2). The contours of the epidemic curves were also strikingly different in certain of the States reporting large numbers of cases. In North Carolina the epidemic started in April, but in Minnesota and Iowa it began a month to 6 weeks later. However, the general outlines of the curves for these three States are similar. In each instance there was a fairly rapid rise to a peak in 10 to 12 weeks, for the States as a whole, and then a more gradual decline. In Texas there was an increase in incidence in late March, principally in the lower Rio Grande Valley and later in the northern part of the State which accounts for the sustained appearance of the outbreak in that State. Since only a small proportion of this large State had epidemic prevalence, the morbidity rates by weeks were never very high.

In California poliomyelitis became epidemic in late May and June, first in Los Angeles and San Diego Counties and later in more northerly sections, which accounts for a rather flat curve. In South Dakota the epidemic had the appearance of an explosive outbreak, and the peak of incidence was not reached there until late October. The beginning of epidemics at various times in different sections makes the curve for the entire United States somewhat different from other years (1946 for instance, which is shown in figure 2 for comparison). The slight hump in the ascending portion of the curve for 1948 appears to be the result of the early appearance of the disease in North Carolina and Texas. However, the decline seems to have been no different from former years.

Trends in morbidity in certain States. Various statements have been made in recent years to the effect that poliomyelitis is actually increasing in the United States, such assumptions presumably being based on the fact that the total number of cases reported in recent years exceeds that for any previous period. Part of this increase in number is undoubtedly due to a better recognition of cases, more

complete reporting, and the inclusion of many more nonparalytic cases (which has been pointed out on numerous occasions in previous reports by the author).

Using only total numbers of cases reported without regard to any of the factors just mentioned, it does appear that incidence is increasing in some States, especially in southern and western sections of the country. However, in other States, particularly in the northeast, the trend of incidence rates over the past 3 decades is actually downward, and in still other States there appears to have been no increase or

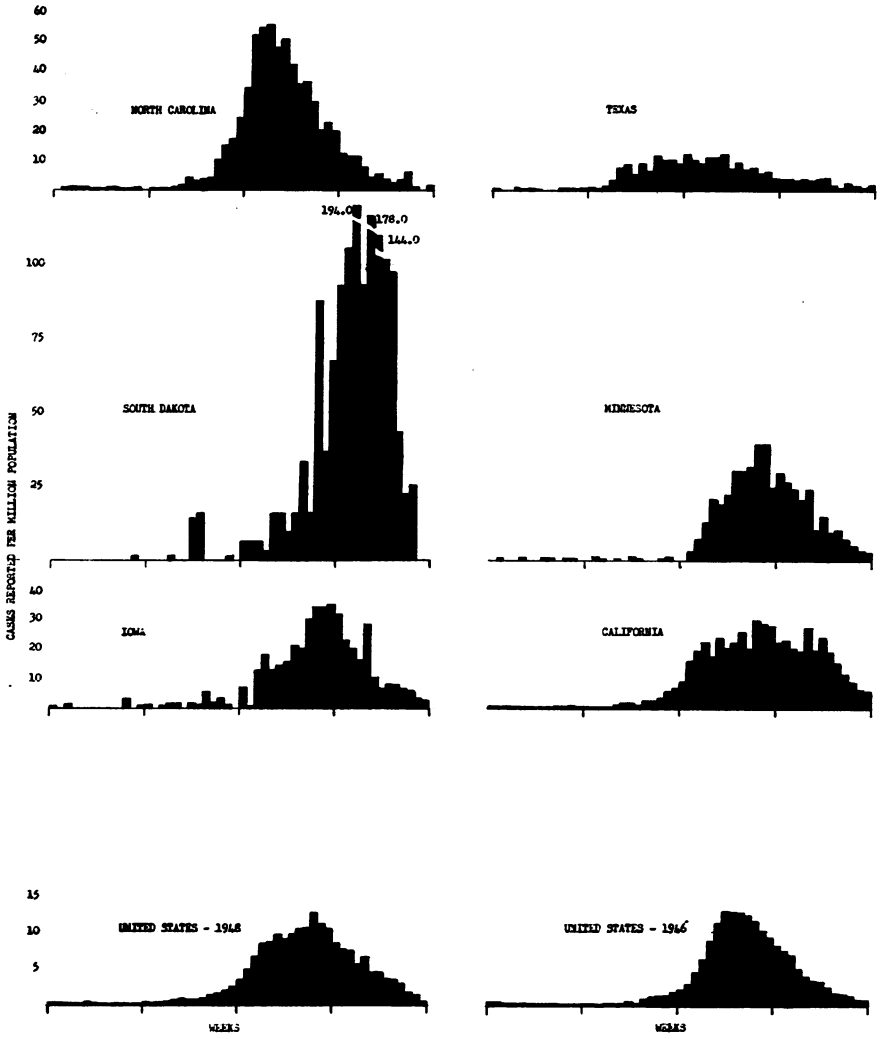

Figure 2. Poliomyelitis morbidity rates per million population by weeks in eight States in 1948 and in the United States in 1946 and 1948.

decrease. The trend of incidence rates is shown (fig. 3) for several States selected to show different types of trends. For instance, in Massachusetts and Vermont the general trend has been definitely downward, and in Kansas and California the opposite sort of trend is apparent. In Pennsylvania and Maryland the downward trend is evident but less marked as compared with Massachusetts, and the upward trend in Michigan and Mississippi is slight compared with Kansas and California.

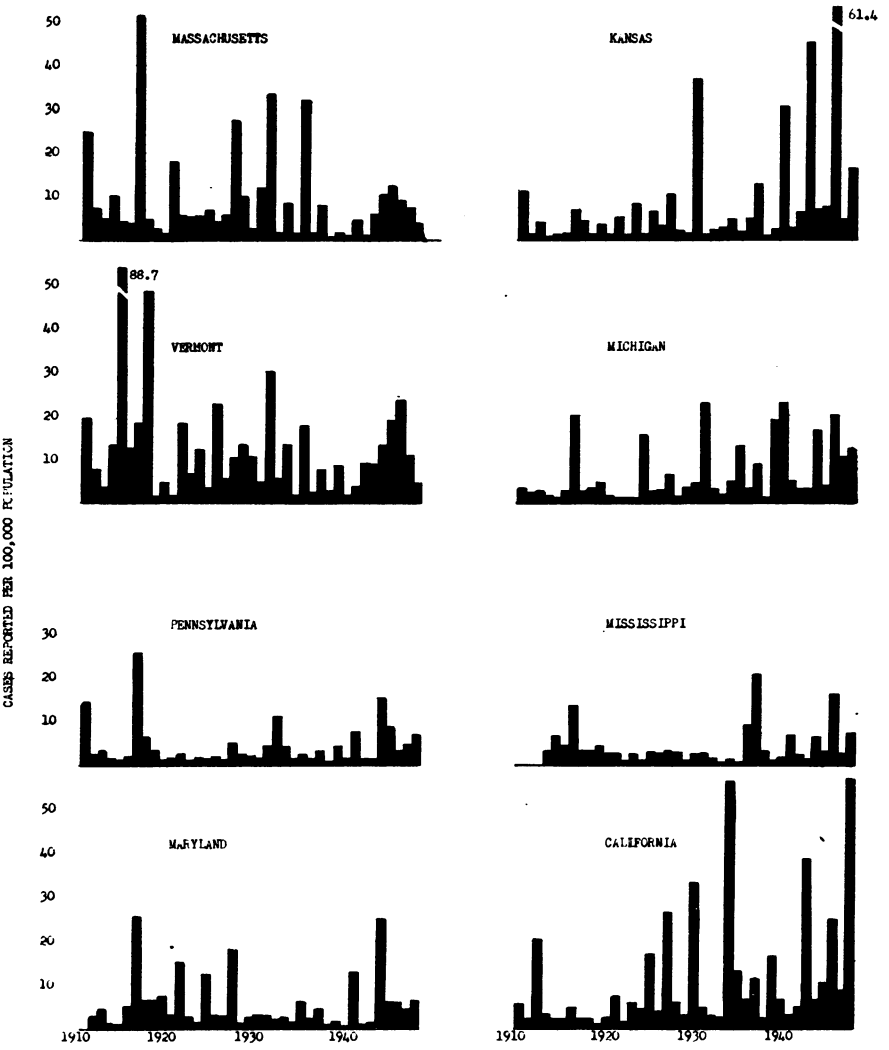

Figure 3. Poliomyelitis morbidity rates per 100,000 population by years in eight States, 1910–1948.

In previous reports the author has used the ratio of cases reported to deaths registered as an index of relative completeness of reporting of poliomyelitis. It is worth noting that these ratios have shown similar changes in States which show upward trends in incidence when compared with those having downward trends. Thus, in Kansas the ratio of cases reported to deaths registered increased from 3.1 (1910–19) to 10.7 (1937–46), and in California the ratio increased from 3.5 to 14.2 in a similar period of time. On the other hand in Massachusetts the ratio changed from 4.5 to 17.0, and in Vermont from 5.5 to 10.1 in the same periods of time, which suggests that completeness of reporting probably does not explain the downward trend in some States as compared to the upward trend in others.

Prevalence in foreign countries. Poliomyelitis was epidemic in various parts of the world in 1948. An outbreak occurred in April in the Reynosa district in the lower Rio Grande Valley of Mexico, which is opposite the area in Texas where the disease first began to appear late in March. Twelve cases with 1 death were reported in the Reynosa district up to May 26. Incomplete reports indicate that the disease was prevalent later in Mexico City, 15 cases being reported during the week ending November 6. Reports from Maracaibo, Venezuela, where 8 cases were reported in 1 day during May, suggests that an epidemic occurred in that area. The capital of Nicaragua also reported a number of cases in December 1948.

In New Zealand an epidemic began in November 1947 which normally is the season when the disease is most prevalent. From November 1947 to March 1948, 303 cases with 18 deaths were reported. However, the prevalence continued to be relatively high throughout 1948—1,170 cases with 50 deaths being reported. In the Auckland area, it was reported that the ratio of suspect to positive cases was 300 to 1, and the ratio was higher in persons 15 and over than in those under 15 years. A slightly higher percentage of cases was under 5 years of age (30.6 percent) in the Auckland area than was reported for all of New Zealand (24.4 percent). About 36 percent of 275 cases reported between November 1947 and March 1948 were classified as nonparalytic. The disease also was prevalent in Australia during 1948, 460 cases being reported from January through September.

An outbreak was reported in the Netherlands Indies. The 51 cases with 5 deaths between August and November were said to have occurred in all races but principally in children. In 1946, 198 cases of poliomyelitis were reported in the Netherlands Indies. In Singapore, 138 cases with 21 deaths were reported from April 17 to October 30, 1948. Of 76 cases reported up to May 25, 30 were adults: 13 European, 11 Chinese, 3 Malay, and 1 each for Indians, Eurasians, and

Ceylonese. Among the 46 cases in children, 31 were Chinese. In the Federated Malay States, 133 cases with 11 deaths were reported in 1948 from May through October. At the same time there was an increase in incidence in Ceylon, 145 cases with 8 deaths being reported from May 23 to October 23, with 30 additional cases in the following 2 months. Late in 1948 and extending into 1949, an increase was reported on the Island of Mauritius. The last previous epidemic on this island occurred in 1945.

Iceland reported poliomyelitis to be prevalent in 1948, principally in one district where 125 cases were reported through November.

INCIDENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDING MAY 21, 1949

A total of 101 cases of poliomyelitis was reported during the week, as compared with 85 last week, 126 for the corresponding week last year, and a 5-year (1944–48) median of 47. The largest increase, 14 cases last week to 42 currently, occurred in Texas. The 4 other States reporting more than 3 cases each are California 11 (last week 9), Mississippi 5 (last week 1), Louisiana 5 (last week 4), and Colorado 4 (last week 1). In Oklahoma, where 8 cases occurred last week, only 3 cases were reported currently. The total reported since March 19 (average seasonal low week) is 541, as compared with 589 for the same period last year and a 5-year median of 299.

The reported incidence of measles declined for the country as a whole and in all geographic divisions except for an increase in the Middle Atlantic area from 6,154 cases last week to 6,878 currently, and slight increases in the West North Central and Mountain areas. The total to date is 481,500, 5-year median 393,154.

Of 26 cases of Rocky Mountain spotted fever reported (last week 22, 5-year median 14), 12 occurred in the South Atlantic area (6 in Virginia), 6 in the Mountain area, 4 in the North Central, 3 in the South Central, and 1 in California. The total for the year to date is 83. The largest comparable figure of the past 5 years is 56, reported in 1946.

During the current week five cases of smallpox were reported, three in Missouri and one each in Wisconsin and Colorado. Two cases of anthrax were reported in New York.

The current figures for diphtheria, meningococcal meningitis, scarlet fever, typhoid fever, and whooping cough are well below the respective 5-year medians.

Deaths recorded during the week in 94 large cities in the United States totaled 8,871, as compared with 8,973 last week, 8,781 and 8,956 for the corresponding weeks of 1948 and 1947, and a 3-year (1946–48) median of 8,894. The total for the year to date is 193,305, as compared with 197,402 for the corresponding period last year. Infant deaths during the week totaled 592, as compared with 611 last week and a 3-year median of 639. The total to date is 13,070, same period last year 13,762.

Telegraphic case reports from State health officers for week ended May 21, 1949

[Leaders indicate that no cases were reported]

Division and State	Diphtheria	Encephalitis, infectious	Influenza	Measles	Meningitis, meningococcal	Pneumonia	Poliomyelitis	Rocky Mt. spotted fever	Scarlet fever	Smallpox	Tularemia	Typhoid and paratyphoid fever	Whooping cough	Rabies in animals
NEW ENGLAND														
Maine			1	344		10	1		4			2	23	
New Hampshire			1	69		1							5	
Vermont			3	76					7					
Massachusetts	11			545	3				155				117	
Rhode Island				80		2			12				2	
Connecticut	1			936	2	31			21				6	
MIDDLE ATLANTIC														
New York	5	2	[c]3	2,461	9	392	2		[d]180			3	173	5
New Jersey	3		5	2,052	1	57			87			1	69	1
Pennsylvania	2		(c)	2,365	9		2		173			2	97	6
EAST NORTH CENTRAL														
Ohio	3		1	1,840	1	54	1		162			3	67	12
Indiana	4	2		154	1	6		1	32		1	1	21	20
Illinois	3		6	240	5	80	2	1	80		3	1	58	2
Michigan [a]	2	3		602	2	42	2		200			2	36	
Wisconsin		1	1	2,163	2	1			41	1			26	
WEST NORTH CENTRAL														
Minnesota	1			165	1	11	1		25			2	2	
Iowa	3			[b]133		1	[b]1		16				4	14
Missouri		1	1	142		17	2	2	26	3			3	
North Dakota			10	79			1		2				2	0
South Dakota	1			106					2					
Nebraska			4	310	1	2			13			2		
Kansas			14	334		12			8		1			
SOUTH ATLANTIC														
Delaware				40					5					
Maryland [a]			2	141		57			[d]32				12	
District of Columbia	1			57	1	6			5			1	2	
Virginia	2		65	608	1	26		6	6		1	4	49	3
West Virginia	2		14	89		4			11			1	16	
North Carolina	2			636	3		3	2	16				14	
South Carolina	8		242	529		100		3			1	4	25	4
Georgia	3		16	295		31		1	10		2	1	5	9
Florida	2	4		153	4	3	3		4			1	1	

EAST SOUTH CENTRAL														
Kentucky	2	1		240	6	17			19			3	4	18
Tennessee	1		33	312	5	51	1	2	14		1	1	25	
Alabama	3		30	337	1	48	3		2			3	11	10
Mississippi [a]	1		4	57		21	5		6		2	1	3	
WEST SOUTH CENTRAL														
Arkansas	1		26	430		18	2	1	1		5	1	10	
Louisiana	7		2	19	1	4	5		4			1	2	
Oklahoma	2		17	184	1	28	3		2		1			2
Texas	11	2	535	1,275	9	249	42		21			11	135	21
MOUNTAIN														
Montana				306					11				3	
Idaho			18	207		7		1	[d] 9					
Wyoming				13		2		1	2		2	1	3	
Colorado	1			272		21	4	4	8	[2] 1		2		
New Mexico		1	3	149	1	33			4				7	
Arizona	2		38	144	1	23			4				6	
Utah [a]	1	1		99			2		7				37	
Nevada														
PACIFIC														
Washington	1		3	618	1	3	1		22				11	
Oregon	1		7	147	1	18	1		21				20	
California	3	1	8	1,082	4	16	11	1	[d] 80			3	85	3
Total	96	19	1,113	23,635	77	1,505	101	26	1,572	5	20	58	1,197	
Median, 1944–48	205	7	909	22,881	93		47	14	3,421	9	17	70	2,026	
Year to date, 20 weeks	3,112	187	69,850	[1] 481,500	1,668	43,742	[1] 1,464	83	51,005	[2] 43	478	899	20,291	
Median, 1944–48	5,217	166	184,505	393,154	3,379		811	46	69,924	204	356	1,029	42,016	
Seasonal low week ends	(27th) July 10		(30th) July 31	(35th) Sept. 4	(37th) Sept. 18		(11th) Mar. 19		(32nd) Aug. 14	(35th) Sept. 4		(11th) Mar. 19	(39th) Oct. 2	
Since seasonal low week	8,226		106,120	[1] 533,893	2,512		541		73,703	[2] 58		439	30,324	
Median, 1943–48 [b]	12,783		327,208	428,100	4,883		299		108,495	282		554	71,899	

[a] Period ended earlier than Saturday.

[b] The median of the 5 preceding corresponding periods; for poliomyelitis and typhoid fever the corresponding periods are 1944–45 to 1948–49, inclusive.

[c] New York City and Philadelphia only, respectively.

[d] Including cases reported as streptococcal infection and septic sore throat.

[e] Including paratyphoid fever; reported separately, as follows: New York 1; Minnesota 2; Georgia 1; Florida 1; Wyoming 1; Colorado 2; California 2. Salmonella infections, not included, were reported as follows: Massachusetts 1; New York 3.

[1] Delayed reports (included in cumulative totals only): Iowa, measles, March 718 cases, April 492 cases; poliomyelitis 1 case, January onset (not included in total since low).

[2] Deduction: Smallpox, 1 case, Colorado, week ended Apr. 30; diagnosis changed.

Anthrax: New York 2.

Alaska: Pneumonia 4; influenza 4; scarlet fever 2; measles 2; meningitis 1; streptococcal sore throat 2.

Hawaii Territory: Influenza 2; measles 99.

TERRITORIES AND POSSESSIONS

Puerto Rico

Notifiable diseases—4 weeks ended March 26, 1949, and 5 weeks ended April 30, 1949.—During the 4 weeks ended March 26, 1949, and the 5 weeks ended April 30, 1949, cases of notifiable diseases were reported in Puerto Rico as follows:

Disease	Cases		Disease	Cases	
	4 weeks ended Mar. 26, 1949	5 weeks ended Apr. 30, 1949		4 weeks ended Mar. 26, 1949	5 weeks ended Apr. 30, 1949
Chickenpox	186	259	Syphilis	147	93
Diphtheria	31	24	Tetanus	3	20
Dysentery, unspecified	3	3	Tetanus, infantile	1	4
Gonorrhea	192	166	Tuberculosis (all forms)	314	540
Influenza	84	72	Typhoid fever	3	1
Malaria	52	44	Typhus fever (murine)	3	2
Measles	86	66	Whooping cough	559	830

DEATHS DURING WEEK ENDED MAY 14, 1949

[From the Weekly Mortality Index, issued by the National Office of Vital Statistics]

	Week ended May 14, 1949	Corresponding week, 1948
Data for 94 large cities of the United States:		
Total deaths	8,973	9,422
Median for 3 prior years	9,390	
Total deaths, first 19 weeks of year	184,434	188,621
Deaths under 1 year of age	611	746
Median for 3 prior years	746	
Deaths under 1 year of age, first 19 weeks of year	12,478	13,172
Data from industrial insurance companies:		
Policies in force	70,402,753	71,062,649
Number of death claims	12,656	12,976
Death claims for 1,000 policies in force, annual rate	9.4	9.5
Death claims per 1,000 policies, first 19 weeks of year, annual rate	9.7	10.3

FOREIGN REPORTS

CANADA

Provinces—Notifiable diseases—Week ended April 30, 1949.—During the week ended April 30, 1949, cases of certain notifiable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Chickenpox		21	1	238	581	19	47	45	161	1,113
Diphtheria				2	1	1				4
Dysentery, bacillary				3					1	4
German measles		3		503	46	2	92	38	20	704
Influenza		77			11	7	100			195
Measles		184	23	128	281	131	113	252	281	1,393
Meningitis, meningococcal						1				1
Mumps		53	5	75	439	49	16	2	65	704
Poliomyelitis						3				3
Scarlet fever		4	1	91	62	2		9	9	178
Tuberculosis (all forms)		6	13	97	64	24	6	13	70	293
Typhoid and paratyphoid fever			1	14	1					16
Undulant fever				2	1					3
Venereal diseases:										
Gonorrhea		9	15	92	62	44	18	33	51	324
Syphilis		3	9	64	40	4	5	8	9	142
Other forms									1	1
Whooping cough		12		72	18	2	9	1		114

NEW ZEALAND

Notifiable diseases—4 weeks ended March 26, 1949.—During the 4 weeks ended March 26, 1949, certain notifiable diseases were reported in New Zealand as follows:

Disease	Cases	Deaths	Disease	Cases	Deaths
Cerebrospinal meningitis	4		Poliomyelitis	98	3
Diphtheria	15		Puerperal fever	6	
Dysentery:			Scarlet fever	94	
Amebic	4		Tetanus	1	1
Bacillary	13		Trachoma	2	
Erysipelas	12		Tuberculosis (all forms)	170	34
Food poisoning	15		Typhoid fever	17	
Lead poisoning	1		Undulant fever	3	1
Malaria	2				

CUBA

Habana—Notifiable diseases—4 weeks ended March 26, 1949.—During the 4 weeks ended March 26, 1949, certain notifiable diseases were reported in Habana, Cuba, as follows:

Disease	Cases	Deaths	Disease	Cases	Deaths
Chickenpox	19		Smallpox	1	
Diphtheria	20		Tuberculosis	9	
Malaria	1		Typhoid fever	6	
Measles	15	1			

Provinces—Notifiable diseases—4 weeks ended March 26, 1949.—During the 4 weeks ended March 26, 1949, cases of certain notifiable diseases were reported in the Provinces of Cuba as follows:

Disease	Pinar del Rio	Habana [1]	Matanzas	Santa Clara	Camaguey	Oriente	Total
Cancer	3	21	18	21	2	20	85
Chickenpox		22	15	3	2	42	84
Diphtheria		22	1	1	1	4	29
Leprosy		1					1
Malaria	2	3			1	13	19
Measles		15	1		2	1	19
Smallpox		1					1
Tuberculosis	4	20	5	21	17	14	81
Typhoid fever	4	9	3	6	6	50	78
Undulant fever		1			1	2	4
Whooping cough		20					20

[1] Includes the city of Habana.

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

Note.—The following reports include only items of unusual incidence or of special interest and the occurrence of these diseases, except yellow fever, in localities which had not recently reported cases. All reports f yellow fever are published currently.

A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday in each month.

Cholera

Siam—Bangkok.—Information dated May 19, 1949, reports an outbreak of six cases of cholera in the city of Bangkok, Siam, with one death.

Plague

Belgian Congo—Stanleyville Province.—Plague has been reported in Stanleyville Province as follows: On March 30, 1949, one fatal case in Gobi, a village west of Blukwa; on April 27, 1949, one fatal case in the village of Pitchu, southwest of Blukwa.

India—Calcutta.—Plague has been reported in Calcutta, India, as follows: Week ended April 23, 1949, 44 cases, 4 deaths; week ended April 30, 42 cases, 5 deaths; week ended May 7, 20 cases, 4 deaths.

Indochina (French)—Cochinchina.—During the period April 1–30, 1949, 21 fatal cases of plague were reported in Cochinchina, French Indochina (including cases of pneumonic plague). During the week ended April 30, 2 cases were reported in Saigon-Cholon.

Portugal—Azores—St. Michaels Island.—During the week ended March 26, 1949, one case of plague was reported at Rabo de Peixe, Ribeira Grande, on St. Michaels Island in the Azores.

Smallpox

Colombia.—During the month of March 1949, 329 cases of smallpox were reported in Colombia.

Ecuador.—During the month of March 1949, 65 cases of smallpox were reported in Ecuador.

Great Britain—England and Wales.—Information dated May 20, 1949, states that on May 11, 1949, two new cases of smallpox were reported at Liskeard in Cornwall. Both cases are said to be contacts of the original case reported there the week before (which proved fatal, and in which contact with cases reported from the *Mooltan* had not been established). These three cases in Liskeard are the only cases reported that have not been definitely traced to passengers or members of the crew of the steamship *Mooltan*, or to direct contacts with them.

Ivory Coast.—During the period April 21–30, 1949, 74 cases of smallpox were reported in Ivory Coast.

Java—Batavia.—During the week ended May 14, 1949, 246 cases of smallpox were reported in Batavia, Java.

Typhus Fever

Afghanistan—During the period March 1–31, 1949, 1,191 cases of typhus fever were reported in Afghanistan.

Colombia—During the month of March 1949, 269 cases of typhus fever were reported in Colombia.

Ecuador.—During the month of March 1949, 21 cases of typhus fever were reported in Ecuador.

Pakistan—Northwest Frontier Province.—During the period April 1–30, 1949, 180 cases of typhus fever, with 38 deaths, were reported in Northwest Frontier Province, Pakistan.

Ethiopia.—During the period January 15–February 26, 1949, 115 cases of typhus fever were reported in Ethiopia, 105 of which were stated to have occurred in Shoa Province.

Yellow Fever

No reports of yellow fever were received during the current week.

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