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Methods for the surveillance of endemic treponematoses and sero-immunological investigations of "disappearing" disease

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Although the treatment of whole communities with long-acting penicillin for the control of endemic treponematoses of childhood during the past twenty years has led to a remarkable initial regression of disease, early clinical yaws has not yet been eliminated in large endemic areas and the elimination of early childhood syphilis has been observed in favourable environmental conditions in a single instance only. In most areas, transmission of infection continues at varying levels and recrudescence or periodic focal outbreaks continue to occur.

Mass penicillin campaigns have been undertaken in 46 countries and up to the end of 1970 some 160 million people had been examined and some 50 million clinical cases, latent cases, and contacts had been treated. In the past few years, sero-epidemiological studies of the changing pattern of disease and infection have become possible and methods for long-term surveillance of endemic treponematoses have been developed. The application of these methods to the study of " disappearing " disease is described, particularly with regard to yaws but also to childhood syphilis and pinta.

It is now twenty years since penicillin was introduced into programmes for treating endemic treponematoses of childhood, which are prevalent in rural areas of many developing countries. Preparations such as benzathine benzylpenicillin and PAM[6] were shown to give rise to effective blood and tissue concentrations for 2–3 weeks following single intramuscular injections. Long-acting treatment became available for use on clinical and epidemiological indications, and organized community-wide campaigns could be undertaken in endemic areas.

On the basis of pilot studies of yaws in Haiti (Levitan, 1953), endemic childhood syphilis in Yugoslavia (Grin, 1952), and pinta in Mexico (Edmundson, 1953), mass penicillin campaigns were undertaken by health administrations in 46 countries in the context of the WHO treponematoses programme. Fig. 1 shows the geographical distribution and extent of endemic treponematoses of childhood 20 years ago. Up to 1970, some 160 million people had been examined and some 50 million clinical cases, latent cases, and contacts had been treated in these campaigns. In the first decade, attention was focused on programme application and on the control of disease (Hackett & Guthe, 1956). With declining clinical prevalence of treponematoses, the emphasis changed towards concurrent surveillance. In the last few years sero-epidemiological studies of the changing pattern of disease and infection became possible, and methods for the long-term surveillance of endemic treponematoses have been developed. This article deals with the application of these methods and the study of so-called " disappearing " disease, particularly with regard to yaws; where relevant, reference is also made to endemic childhood syphilis and pinta.

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[6] Procaine benzylpenicillin G in oil with 2% aluminium monostearate.

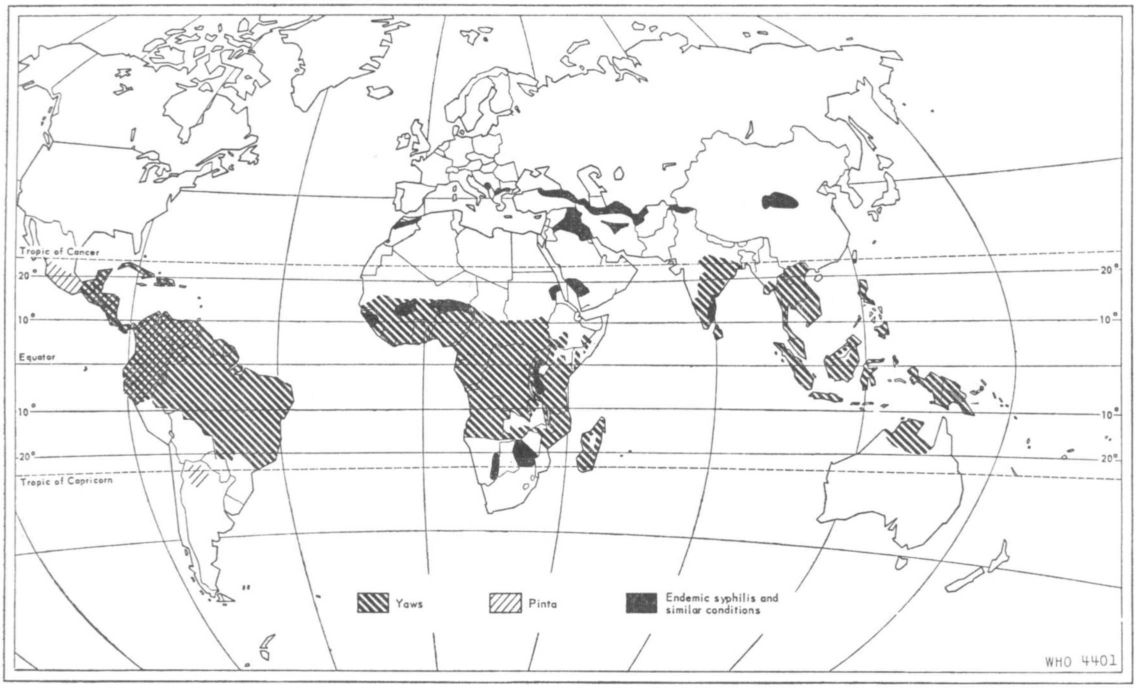


Fig. 1. Geographical distribution of the endemic treponematoses of childhood in the early 1950s.

THE COURSE OF ENDEMIC TREPONEMATOSES

Yaws is a contact disease among children, characterized by crops of highly infectious and relapsing skin lesions in the first 5–6 years of the natural course of the infection. In adolescent and adult life, outbreaks of incapacitating hyperkeratosis occur on the palms and soles, and destructive mutilating lesions of subcutaneous tissues and of bones develop in a large proportion of those infected. By contrast, endemic syphilis involves also mucous membranes, while pinta involves mostly the integument alone.

Fig. 2 identifies the clinical and serological characteristics of infection and disease with regard to transmission and epidemiological importance in a community in which yaws is endemic. The group designations used are those given in the *International nomenclature and classification of yaws* established by WHO (Hackett, 1957). Fig. 2 shows most of the elements that should be included in epidemiological surveillance and considered in relation to time.

Early latent and late latent treponematoses are much more frequent than clinical disease in endemic areas and give rise to periodic infectious relapses and to permanent, late, mutilating lesions. In addition to those with clinical lesions, these latent cases are seroreactive in lipoidal and treponemal antibody tests (e.g., Wassermann, VDRL, fluorescent treponemal antibody (FTA), and treponeme immobilization (TPI) tests).

The serological responsiveness to therapy is a function of the duration of the infection. Seroreactivity is retained throughout life in untreated, infected persons.

MASS CAMPAIGNS AND CONCURRENT SURVEILLANCE

When the therapy of treponematoses depended on multiple injections of arsenicals or bismuth, or both, mass campaigns were attempted against yaws and endemic syphilis in several hyperendemic areas. Treatment surveys and re-surveys were undertaken in rural populations, and information was obtained on the nature, extent, distribution, and pattern of disease. Such concurrent surveillance data on yaws were collected, for example, in Africa (Harding, 1949) and in islands of the Western Pacific area as early as 1923 and again in subsequent years (Buxton,

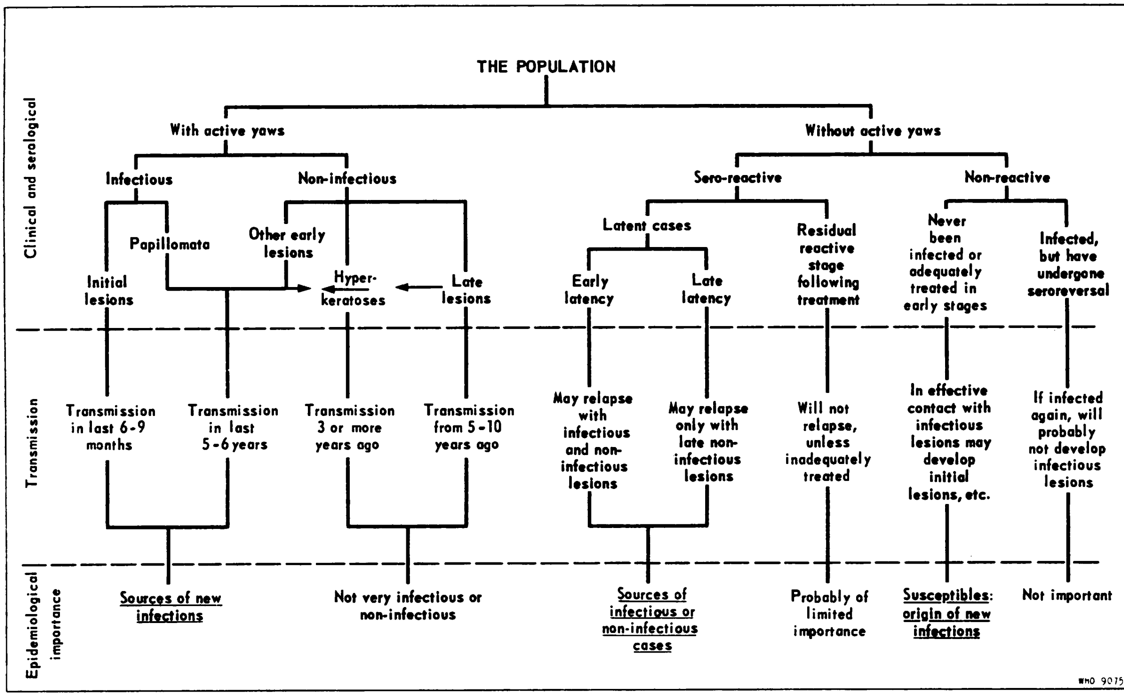


Fig. 2. WHO Treponematoses Programme: population in an endemic yaws community; clinical, serological, and epidemiological characteristics.

1928; Lambert, 1936), while Kogoj & Vuletic (1939) and Grin (1952) obtained data on endemic syphilis in Yugoslavia. However, the epidemiological concept that treatment was also necessary for symptomless household contacts and presumed latent cases, in addition to manifest clinical cases, had not yet evolved. Demographic aspects were not taken adequately into account nor was the epidemiological importance of the population coverage attained in relation to the census population–quantitative aspects that are now considered to be essential elements of mass campaigns and of surveillance.

Several periodic re-surveys are undertaken following the initial treatment survey of mass campaigns against endemic treponematoses. The concomitant surveillance activities represented by these re-surveys serve to establish changing patterns of the disease. The clinical changes are conspicuous and rapid; lesions in individuals with classical early infectious yaws heal within 2–3 weeks following treatment with long-acting penicillin. Considering the regression of infectious lesions in the community rather than in the individual, examples of the large-scale effects are shown in Table 1. The table is arranged in descending order of prevalence of infectious yaws lesions at the beginning of penicillin mass campaigns. The corresponding prevalences at the last re-survey are also shown. Initial prevalences ranged from over 4% in hyperendemic communities of northern Nigeria to 0.1% in the hypoendemic areas in the Philippines. This corresponds to rates of 20% and 1%, respectively, of clinically active yaws in the community when non-infectious cases (not shown in the table) are included.

By comparing the rates at the beginning of the mass campaigns and at the last re-survey, the remarkable fall that takes place following penicillin mass campaigns can be seen. The greatest reduction in yaws occurred in Western Samoa, where the prevalence fell to 0.005%, or 1/600th, of its initial level (Fröhlich & Wang, unpublished data), and northern Nigeria, where it fell to 0.02%, or 1/200th, of its initial level (Antal, unpublished data). In Bosnia, Yugoslavia, the rate of endemic childhood syphilis

Table 1. WHO Treponematoses Programme: prevalence reduction of infectious endemic treponematoses in mass penicillin campaigns, 1954–65, in areas where sero-epidemiological studies were subsequently undertaken. All these programmes concern yaws except in Bosnia, Yugoslavia, where the campaign was directed against endemic syphilis.

Country or area	Period	Rural population involved (millions)	Initial treatment survey (ITS)		No. of re-surveys	Last re-survey level of infectious yaws (%)
			Population coverage at ITS (%)	Infectious yaws (%)		
Northern Nigeria	1954–65	2.65	83	4.2	1–7	0.02
Togo	1956–65	1.50	40	4.1	2–4	0.45
Midwestern Nigeria	1955–64	1.49	77	3.2	2–5	0.18
Western Samoa	1955–61	0.10	96	3.0	5–7 [a]	0.005
Eastern Nigeria	1954–63	6.80	54	1.9	1–5	0.09
Western Nigeria	1956–63	1.90	59	1.8	2–5	0.21 [b]
North-eastern Thailand	1952–60	8.40	50	0.7	2–5	0.09
Southern Thailand	1952–60	3.00	70	0.13	2–5	0.01
Philippines	1952–60	2.40	33	0.1	1–4	0.01
Yugoslavia	1948–54	0.83	80	0.4	1–8	0.00

[a] Includes also a child survey and a sampling survey.
[b] Includes also non-infectious cases.

has been reduced to nil, an observation that will be discussed later. It is noted that the results in these three projects are also associated with the highest population coverages as well as with the greatest number of treatment re-surveys in the mass campaigns (80%, 83%, and 96%, respectively, and up to 8 re-surveys).

From these preliminary findings in the concurrent surveillance of endemic treponematoses the question arises: can early infectious clinical disease actually be eliminated, and can transmission of infection be interrupted by effecting a single rapid change in the environment through community-wide application of a drug, utilized in accordance with the epidemiological characteristics of the disease? To answer this question, detailed data are needed from study areas, and representative sampling investigations in the long-term surveillance of disease and infection must be made.

CHANGING PATTERNS OF DISEASE AND INFECTION AND CHANGING CONCEPTS OF SURVEILLANCE

Before these data are examined it is of interest to consider the changing outlook on surveillance that characterizes the developments in the field of treponematoses. In 1952 epidemiological surveillance data concerning endemic treponematoses were considered at the First International Symposium on Yaws Control held in Bangkok (WHO Expert Committee on Venereal Infections and Treponematoses, 1953). At the Second International Conference on Control of Yaws in 1955 (*Bull. soc. Path. exot.*, 1956; *J. trop. Med. Hyg.*, 1957) and at the WHO Expert Committee in 1952 and 1959 (*Bull. Wld Hlth Org.*, 1953; WHO Expert Committee on Venereal Infections and Treponematoses, 1960), the nature and extent of surveillance in the context of operational activities against yaws were outlined. The rapid decline in prevalence of clinical yaws owing to community-wide use of long-acting penicillin led to the gradual replacement of the concept of " active " concurrent surveillance by one of post-campaign, long-term surveillance, not necessarily associated in time with immediate, operational action. However, " watchful scrutiny " was exercised in more detailed studies of the changing patterns of disease (clinical), as well as of infection (immunological), resulting from the environmental change effected by community-wide treatment with penicillin. Epidemiological data were gradually obtained for study, review, and evaluation, as a basis for subsequent action considered by the health authorities to be possible under the new circumstances. This strategy is in line with the general principles of surveillance for communicable diseases advocated by Langmuir (1963), Raska (1966), and others and, more recently, emphasized in the Technical Discussions at the Twenty-first World Health Assembly and by the WHO Scientific Group on Treponematoses Research (1970).

The changing approach to the surveillance of yaws was taken into account, with other developments, in the technical policy of WHO for the guidance of yaws campaigns. With decreasing clinical prevalence of disease in any one field there is classically an increasing need for the introduction of more refined laboratory measurements of infection in addition to indices of overt clinical disease. In the surveillance of yaws, extensive use of immunological methods became necessary at the same time as representative sampling techniques were introduced for use in large rural tropical populations. Only limited facilities for laboratory testing and sampling exist in many developing countries and WHO undertook to promote the surveillance of yaws by establishing international epidemiological research teams. Thus, after 1960, WHO developed a sero-epidemiological survey technique for evaluating the long-term results of mass campaigns, for promoting long-term, post-campaign surveillance, and for acquiring information about yaws as a " disappearing " disease.

Endemic treponematoses, notably yaws, therefore illustrate well a concept changing from (1) " active " concomitant surveillance when prevalence of the disease is high, transmission frequent, and indices predominantly clinical, such surveys being carried out at a time when an extensive field team can be mobilized for operational activities, to (2) long-term, post-campaign surveillance, emphasizing evaluation, when prevalence is low, transmission less frequent, and indices predominantly serological, and when methodological aspects are important for the epidemiological study of " disappearing " disease. This would be carried out at a time when national operational field teams could not continue to be available for treponematoses surveys alone because of the reduction in prevalence resulting from the mass treatment programme. Similar changes in surveillance patterns have occurred in the world-wide malaria and smallpox eradication programmes sponsored by WHO.

Detailed data are available from clinical and sero-immunological sampling investigations in study areas to illustrate the long-term aspects of the environmental changes represented by community-wide treatment with penicillin.

(1) Data on the regression of infectious yaws from Western Samoa (Table 2), for example, cover a

Table 2. Effectiveness of the penicillin mass campaign in Western Samoa; reduction in prevalence of active yaws on successive surveys between 1955 and 1965/66. Data from the WHO Treponematoses Programme

Survey		Population		Clinically active yaws (%)	
		Estimated (thousands)	Percentage examined	Infectious	Total
Initial treatment survey 1955		96.9	96.7	2.950	11.044
Resurveys					
1st	1956	97.0	61.9	0.021	0.064
2nd	1957	100.2	99.6	0.028	0.036
3rd	1958	100.2	95.0	0.012	0.012
4th	1959	103.0	95.6	0.011	0.011
5th	1960	108.8	92.4	0.005	0.005
6th	1961	110.0	26.1 [a]	0.028	0.028
7th	1965/66	113.0	9.1 [b]	0.010	0.010

[a] Children under 15 years only.
[b] Random sample survey.

Table 3. WHO Treponematoses Programme: epidemiological sampling studies (clinical and immunological) 7–20 years following initial treatment surveys of mass penicillin campaigns against endemic treponematoses. These studies concern yaws except in Bosnia, Yugoslavia, where the campaign was directed against endemic syphilis

Country or area	Sampling survey period	Selected sample coverage (%)	No. of sampling points	No. of persons clinically examined	Infectious yaws (%)	No. of persons serologically examined	Seroreactors (%)
Northern Nigeria	1965–66	95.3	48	7 621	0.07	3 802	21.7
Togo	1963–66	96.3	22	16 171	0.11	7 617	21.9
Midwestern Nigeria	1966–67	92.4	15	2 991	0.23	1 329	26.1
Western Samoa	1965–66	97.3	32	7 839	0.01	2 788	16.2
Eastern Nigeria	1963–64	91.9	56	8 824	0.07	4 201	22.6
Western Nigeria	1966–67	87.3	22	3 691	0.36 [a]	1 563	7.2
North-eastern Thailand	1960–61	91.4	24	22 744	0.11	11 935	32.2
Southern Thailand	1961–62	87.3	16	15 538	0.06	7 320	23.2
Philippines	1962–63	90.2	37	16 024	0.04	8 001	13.1
Yugoslavia (Bosnia)	1968–69	80.0	48	9 629	0.00	9 534	1.1

[a] Includes also non-infectious cases.

10-year period with 7 re-surveys between 1955–56 and 1966. A reduction of infectious lesions to 0.021%, or less than 1/100th, of their previous level, had already been achieved at the time of the first re-survey in 1956, i.e., within 1 year. At the fifth re-survey (1960) a rate of 0.005% of infectious cases had been established. The sixth re-survey (1960) was a special survey among children (the main group at risk) in whom the rate was then 0.028%. The seventh re-survey in 1965 was a representative sampling survey throughout the country; the rate of infectious yaws had now doubled by comparison with the last complete island-wide re-survey in 1960. The long-term surveillance data suggest therefore that the disease had not reached a level leading to self-extinction.

(2) Representative clinical, as well as immunological, sampling studies have been undertaken in the long-term surveillance of endemic treponematoses (Table 3) 7–20 years after the beginning of the mass campaigns. Data in this table correspond to the mass campaign examples included in Table 1. As already mentioned, infectious yaws lesions now range from 0.23% in mid-western Nigeria (Ruland, unpublished data) to 0.01% in Western Samoa. In all but two instances, these yaws rates are higher than at the last re-survey of the mass campaigns (see Table 1). In endemic syphilis in Bosnia, the rate of infectious lesions remained at nil 15 years after the last re-survey. With regard to serological findings, prevalences will generally be seen to be high—up to 32.2% in north-eastern Thailand (Christiansen, unpublished data). These overall rates are, however, of limited value, since with rapid extinction of early clinical lesions in the community, attention becomes increasingly focused on sero-immunological age patterns of infection and not only on clinical disease.

SERO-IMMUNOLOGICAL STUDIES, PERSISTENT INFECTION, AND LONG-TERM SURVEILLANCE

Examples of age-specific seroreactor rates in representative areas at different levels of endemicity of treponematoses prior to the introduction of penicillin mass campaigns are shown in Fig. 3. The sero-immunological community profiles are characteristic for hyperendemic, mesoendemic and hypoendemic areas. The great force of infection in hyperendemic areas is reflected in the steep rise of the seroreactor curve to 80–90% in the younger age groups in hyperendemic yaws and endemic syphilis areas. A slow rise to more moderate seroreactor levels of 35–65%

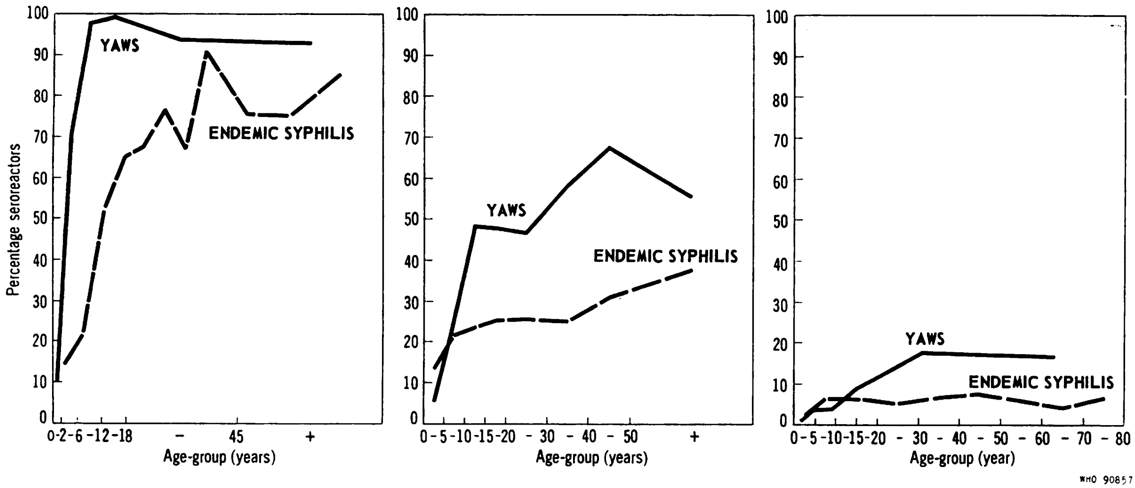


Fig. 3. Examples of age-specific seroreactor rates in endemic treponematoses at different levels of endemicity prior to mass penicillin campaigns. The seroreactor rates were determined by lipoidal antigen (VDRL) tests. Little or no arsenical treatment had previously been applied in the study areas. A, Hyperendemic areas: yaws study—Asmath, West Irian, 1956 (population 1 680); endemic syphilis study—Deir er Zor, Syrian Arab Republic, 1955 (population 1 172). B, Mesoendemic areas: yaws study—Gaeyai, Thailand, 1953 (population 6 409); endemic syphilis study—Sapna, Bosnia, Yugoslavia, 1953 (population 3 352). C, Hypoendemic areas: yaws study—Moejoe, West Irian, 1956 (population 14 599); endemic syphilis study—Zwornik, Bosnia, Yugoslavia, 1950 (population 2 679). Data from the WHO Treponematoses Programme.

in the community characterizes the mesoendemic profile, and a very slow rise to low levels of seroreactors up to 20% characterizes the hypoendemic areas.

Hyperendemic areas

The sero-immunological age profile in Western Samoa at the beginning of the mass campaign in 1955 is shown in Fig. 4. The proportion of seroreactors rises very rapidly in the early years of life, each group accumulating seroreactors of the preceding age groups, indicating the great force of infection. The rise of the curve corresponds to an average annual infection rate of 5.5% up to the age of 15 years. From a maximum of about 80%, the curve tapers off for the older age groups, the cohorts reflecting the past epidemic situation.

For 1965–66, 10 years after the beginning of the mass campaign, the sero-immunological age profile is different; only 15% of children are now infected at 15 years of age. The minimum sero-prevalence is about 5% among those aged 5–9 years who were born during the first 5 years (1956–60) of the 10 years during which systematic annual treatment re-surveys were undertaken. In the younger (1–4 years) age group the seroreactor rate is higher—namely, about 13%. These are children born during the second 5 years (1961 to 1965–66) of the 10-year period. Clinical data indicating that more infectious clinical cases also occurred in the children, and that the overall rate of infectious lesions doubled in the second 5 years, have already been mentioned.

In hyperendemic areas of northern Nigeria (stratum 1) 12 years after the beginning of the campaign, the sero-immunological age profile is less steep than the hyperendemic pre-campaign model from Western Samoa. A maximum of 68% of seroreactors is reached at about 40 years of age. An indentation in the curve is seen in children under 15 years of age, i.e., those who were born during the mass campaign, indicating its sero-immunological effect. The rate of infectious lesions was 4.6% before, and 0.1% 12 years after, the mass campaign.

In hyperendemic areas of eastern Nigeria 9 years after the beginning of the mass campaign the rise of the curve is considerably steeper and approaches somewhat the pre-campaign model in Western Samoa. The indentation in the curve for young age groups, corresponding to the 9-year mass campaign, is hardly discernible. It will be recalled that the population coverage in this mass campaign was very low—namely, 54%. The rate of infectious lesions was 3.7 % before, and 0.2 % after, the mass campaign.

Fig. 4 shows examples of a well-implemented mass campaign (from a public health point of view), one carried out satisfactorily, and one less adequately carried out.

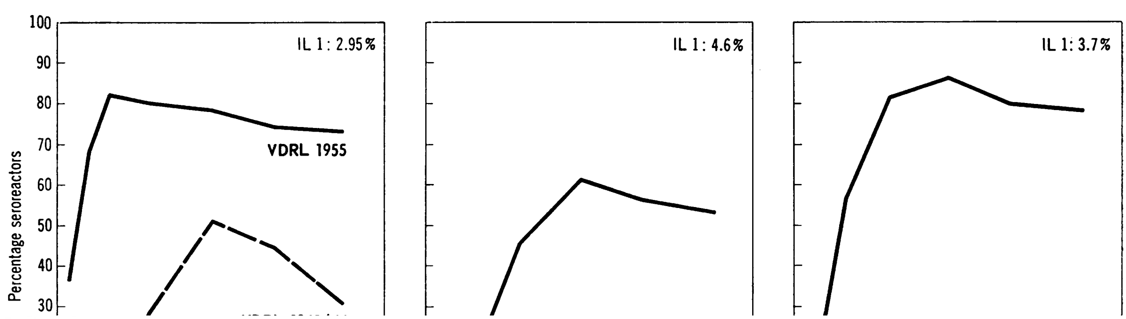
Mesoendemic areas

Sero-immunological characteristics in mesoendemic areas are quite different (Fig. 5). The age profile is shown for Bosnia in 1949, i.e., at the beginning of the mass campaign against endemic childhood syphilis. Seroreactivity among children before the campaign rises relatively rapidly at first. The curve then becomes flatter. About 25 % of children aged 15 years are infected, corresponding to an average annual infection rate of less than 1.5 %. In the adults, seroreactivity continues to rise slowly to a maximum of about 40 % in the older age groups.

The sero-immunological profile 20 years later in 1969 shows no VDRL seroreactors in the children, or in fact in any of the population under 20 years of age; this observation suggests a complete interruption in the transmission of infection. There is a slowly rising residual curve of VDRL seroreactors in the older age groups—i.e., evidence of the past endemic. These are preliminary findings in a current WHO 3-year sero-epidemiological sampling survey. However, using more sensitive and specific methods—namely, FTA and TPI antibody tests—residual seroactors have been found in 0.3 % of the children. These preliminary findings are now being studied further. Careful investigations show that none of these reactive children offers evidence of past or present clinical disease. The possibility of subclinical infection must therefore be considered, and this will be discussed later.

In mesoendemic areas in northern Nigeria (stratum 2), 12 years after the beginning of the yaws mass campaign, there is an indentation in the profile corresponding to those born during the mass campaign. The curve then rises more abruptly to about age 20 years, and then continues to rise slowly, reaching about 45 % in the oldest age groups. The rate of infectious lesions was 0.6 % prior to the mass campaign and nil at the sero-immunological survey in this mesoendemic stratum.

Finally, if mesoendemic areas in Togo are considered, 7 years after the beginning of the mass cam-



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