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 favourale 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 30 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 4 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.
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,
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...
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

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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.

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

a Includes also a child survey and a sampling survey.
b Includes also non-infectious cases.
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>
<thead>
<tr>
<th>Survey</th>
<th>Population</th>
<th>Clinically active yaws (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated</td>
<td>Percentage examined</td>
</tr>
<tr>
<td></td>
<td>(thousands)</td>
<td></td>
</tr>
<tr>
<td>Initial treatment survey 1955</td>
<td>96.9</td>
<td>96.7</td>
</tr>
<tr>
<td>Resurveys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st 1956</td>
<td>97.0</td>
<td>61.9</td>
</tr>
<tr>
<td>2nd 1957</td>
<td>100.2</td>
<td>99.6</td>
</tr>
<tr>
<td>3rd 1958</td>
<td>100.2</td>
<td>95.0</td>
</tr>
<tr>
<td>4th 1959</td>
<td>103.0</td>
<td>95.6</td>
</tr>
<tr>
<td>5th 1960</td>
<td>108.8</td>
<td>92.4</td>
</tr>
<tr>
<td>6th 1961</td>
<td>110.0</td>
<td>26.1</td>
</tr>
<tr>
<td>7th 1965/66</td>
<td>113.0</td>
<td>9.1</td>
</tr>
</tbody>
</table>

* Children under 15 years only.

*b Random sample survey.

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.
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%
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 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 seroreactors 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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**Fig. 4. Sero-immunological profiles 9–12 years after mass penicillin campaigns in previously hyperendemic areas of childhood treponematoses.**

A. Western Samoa: age-specific seroreactor rates (\%) in representative population samples of 6 122 persons examined by VDRL tests in 1955 and 4 990 persons examined by VDRL tests in 1965–66, i.e., 10 years after the initial treatment survey of the yaws mass campaign. Infectious lesions at the 1955 survey, 2.95\%; infectious lesions at the sero-epidemiological study, 0.01\%. B. Northern Nigeria, 1966, stratum 1: age-specific TPI seroreactor rates (\%) in a representative population sample of 4 662 persons 12 years after the initial treatment survey of the yaws mass campaign. Infectious lesions at initial survey, 4.6\%; infectious lesions at sero-epidemiological study, 0.1\%. C. Eastern Nigeria, 1963, stratum 3: age-specific FTA200 seroreactor rates (\%) in a representative population of 2 419 persons 9 years after the initial treatment survey of the yaws mass campaign. Infectious lesions at initial survey, 3.7\%; infectious lesions at sero-epidemiological study, 0.2\%. Data from the WHO Treponematoses Programme.
Fig. 5. Sero-immunological profiles 7–20 years after mass penicillin campaigns in previously mesoendemic areas of childhood treponematoses. A, Bosnia, Yugoslavia: age-specific VDRL seroreactor rates (%) in representative samples of 3,325 persons in 1949 and 9,534 persons in 1969, 20 years after the mass campaign against endemic childhood syphilis. Infectious lesions at initial survey, 0.44%; infectious lesions at sero-epidemiological study, 2.0%. B, Northern Nigeria, 1966, stratum 2: age-specific TPI seroreactor rates (%) in a representative population sample of 2,958 persons 12 years after the initial treatment survey, 0.69%; infectious lesions at sero-epidemiological survey, 2.0%. C, Togo, 1964, stratum 1: age-specific VDRL seroreactor rates (%) in a representative population, sample of 6,291 persons 7 years after the initial treatment survey of the yaws mass campaign. Infectious lesions at initial survey, 1–2%; infectious lesions at sero-epidemiological survey, 0.2%. Data from the WHO Treponematoses Programme.

A considerable proportion of seroreactors with high antibody titres are likely to develop infectious clinical relapse, which may lead to focal outbreaks and the recrudescence of disease. There are several examples of this. In Western Samoa, only 0.6% of the children and 1.6% of the adults had high VDRL titres (1:16 or more), indicating a limited but still existent reactivation (relapse) and recrudescence potential. In mid-western Nigeria 1.7% of the children and 5.9% of adults were found to have high-titre sera, suggesting a greater recrudescence potential than in Western Samoa. In north-eastern Thailand (Warish district), 9.5% of the children and 28.9% of the adults had high-titre sera, suggesting a considerable epidemiological potential. High-titre sera therefore have a certain predictive value in the surveillance and evaluation of mass penicillin campaigns.

SOME METHODOLOGICAL ASPECTS

Before considering the implications of the findings in these studies, some methodological aspects affecting their precision should be discussed:

1. The investigations were undertaken by WHO epidemiological field teams in full co-operation with national health administrations and in close collaboration with special WHO epidemiological research teams, the WHO International Reference Centres for Treponematoses at the Institut Alfred Fournier, Paris, at the State Serum Institute, Copenhagen, and at the Medical Research Council Public Health Laboratory Service (WHO Venereal Diseases Reference Centre), London, and the International Treponematoses Laboratory Center at the Johns Hopkins University School of Medicine, Baltimore, Md., USA. The studies were planned and prepared, and data were collated and analysed by computer at WHO Headquarters in Geneva, in order to ensure the greatest possible uniformity.

2. Methods based on statistical survey designs with stratification by degree of previous exposure and the use of standard protocols were developed for
the representative sampling of rural populations. Careful assessment is made of the precision with which field performance reflects the theoretical design. To obtain sufficient coverage in the blood sampling of small children, a capillary dried-blood drop method was developed as a basis for immunofluorescent antibody testing (Vaisman & Paris-Hamelin, 1965). An example of theoretical sampling and of actual field performance in a sero-immunological study is shown for northern Nigeria in Tables 4 and 5. It is concluded that the field coverage performance was within acceptable limits.

(3) The relative importance of false seroreactors in lipoidal tests (VDRL) increases with declining seroreactor rates in any community. In the context of childhood treponematoses, false seroreactors are more important in the younger age groups (Fig. 6). Specific FTA and TPI treponemal antibody tests were therefore introduced to supplement lipoidal tests. At the same time, the classical difficulties in the collection, preservation, and transport of serum collections in tropical countries had to be overcome. Equipment was developed for the preservation and transport of serum by freezing in liquid nitrogen to \(-200^\circ\text{C}\), so that non-contaminated field specimens can reach any laboratory in the inert stage and can be examined at any time without a change in seroreactivity having occurred (Guthe, 1965, 1966).

It is believed that these techniques permit a greater degree of precision than was previously possible for sero-immunological sampling studies in rural populations in developing countries when problems of "disappearing" disease are being investigated.

The extensive serum collections obtained—approaching 250 000 samples—up to 1970 have been used also in other surveys, e.g., the WHO programmes on malaria, viruses, bacterial diseases, human genetics, and epidemiological surveillance (Byčenko & Vorst, 1970; Yale Arbovirus Research Unit, 1967; Guthe & de Vries, unpublished data; Ropartz et al., unpublished data; Vesenjak, unpublished data; Voller & Schindler, unpublished data). Samples are also deposited in the WHO Serum Reference Banks as recommended by the WHO Advisory Committee.

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**Fig. 6.** Age-specific seroreactor rates in representative sero-immunological sampling survey of yaws (stratum 1) in northern Nigeria in 1965–66; results of TPI, FTA (serum), FTA (roundelle), and VDRL tests in 541 sera. Data from the WHO International Reference Centre for Endemic Treponematoses, Paris.
Table 4. Survey methodology in rural endemic yaws areas; example of theoretical sampling fraction and of field coverage performance in sero-epidemiological study, northern Nigeria, 1965–66. Coverage requirements according to the sampling design.

<table>
<thead>
<tr>
<th>Population group</th>
<th>Clinical sample</th>
<th>Serological subsample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Venous blood</td>
</tr>
<tr>
<td>children</td>
<td>All registered in selected clusters</td>
<td>One-third of subjects clinically examined over 1 year</td>
</tr>
<tr>
<td>adults</td>
<td>All registered in selected clusters</td>
<td>One-fifth of subjects clinically examined</td>
</tr>
</tbody>
</table>

Table 5. Survey methodology in rural endemic yaws areas; example of theoretical sampling fraction and of field coverage performance in sero-epidemiological study, northern Nigeria, 1965–66. Actual field coverage achieved. Data from the WHO Treponematoses Programme.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of persons registered according to survey design</th>
<th>Clinical sample</th>
<th>Serological subsample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Absent</td>
<td>Examined</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>349</td>
<td>11</td>
<td>338</td>
</tr>
<tr>
<td>1–4</td>
<td>1 273</td>
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<td>1 232</td>
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<td>1 202</td>
</tr>
<tr>
<td>10–14</td>
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<td>520</td>
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<tr>
<td>children</td>
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<td>3 292</td>
</tr>
<tr>
<td>15–29</td>
<td>2 246</td>
<td>172</td>
<td>2 074</td>
</tr>
<tr>
<td>30–44</td>
<td>1 425</td>
<td>114</td>
<td>1 311</td>
</tr>
<tr>
<td>45–59</td>
<td>626</td>
<td>35</td>
<td>591</td>
</tr>
<tr>
<td>≥ 60</td>
<td>374</td>
<td>22</td>
<td>352</td>
</tr>
<tr>
<td>adults</td>
<td>4 671</td>
<td>343</td>
<td>4 328</td>
</tr>
<tr>
<td>unknown</td>
<td>60</td>
<td>59</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>8 218</td>
<td>597</td>
<td>7 621</td>
</tr>
</tbody>
</table>

* Computed on the number of children in the 1–14 years age group.

on Medical Research in 1962. Altogether, 14 laboratories in 9 countries have been involved in collaborative programmes in the field of treponematoses since 1960.

ENVIRONMENTAL CHANGES AND RESEARCH ORIENTATION

On the basis of the survey results, it is now possible to answer more fully the initial question: 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 the community-wide application of a drug?

"The clinical evidence indicates that early infectious yaws in large rural populations can be rapidly and impressively reduced to very low levels, particularly where persistent and systematic measures are undertaken." The long-term studies show that "in no large area... has early infectious clinical yaws been eliminated. Residual..." 

cases and focal outbreaks continue in areas followed up for 10 years or more. Concerning endemic syphilis in Bosnia, where progressive broad environmental changes have favoured the host, there is evidence after 20 years that early clinical disease has been eliminated."

"The immunological evidence indicates that there is a much greater force of infection in areas where yaws is endemic than can be detected solely from clinical indices in prevalence investigations. Following mass campaigns the community seroreactor rates have been reduced slowly in children, and very much more slowly in adults. Even under favourable conditions, the process will take decades. Infection has continued with varying force depending on the conduciveness of the environment to transmission. There is a certain recrudescence potential. Although in Bosnia the non-occurrence of VDRL-seroreactors in persons under 15 years of age suggests that the usual transmission of endemic syphilis has been interrupted, isolated TPI antibody reactivity in some children [born after the mass campaign] points to the possibility of subclinical infection. In the older age groups, seroreactor rates reflect past endemicity of the disease."

It was emphasized by the WHO Scientific Group on Treponematoses Research "that these long-term [surveillance] findings are of importance for the further orientation of immunological and epidemiological research into the processes of continued transmission, 'disappearing disease', and interruption of transmission, and that the findings have implications for health administrations."

**Immunological and epidemiological research**

It was noted by the WHO Scientific Group on Treponematoses Research that "Climatological factors (notably aridity and reduced environmental temperature) may antagonize transmission, minimize clinical characteristics, and alter lesional patterns in endemic treponematoses areas. This has been observed in Africa, for example, in the areas between the tropical belt and the Sahara and Kalahari deserts... [Recent] studies suggest that antagonism to transmission created by penicillin mass campaigns might induce developments of a similar nature. The regressive quantitative changes following mass campaigns reduce opportunities for transmission and lead to less frequent passages of the micro-organism in the human host. A number of children born after mass campaigns against endemic treponematoses were found to be TPI-reactive although there was no anamnestic or clinical evidence of treponemal disease and no seroreactivity in the VDRL test. Such findings have been made in northern Nigeria and the Trust Territory of New Guinea (yaws) and in Bosnia (endemic syphilis)."

"These observations must also be seen in relation to the possible presence of modified treponemes in the human host tissues in subclinical infection. This aspect has received recent attention through the discovery by French investigators of treponemes in the lymph glands of wild African baboons (cynomolgus monkeys) that were reactive in the TPI test but not in the VDRL test without concurrent evidence of clinical disease (Fribourg-Blanc et al., 1966)."

It has been shown in the WHO programme that "these treponemes were reactivated after laboratory animal passages and identified with reasonable confidence as *T. pertenue*, giving rise to typical yaws in susceptible monkeys (Serpetjian et al., 1969) and possibly also in seronegative humans (Medina, 1967)."

It is recognized that "the immunological and other processes concerned in the possible adaptation, persistence, and potential reactivation of attenuated treponemes in nature, or following the wide use of relatively small dosages of antibiotics in mass campaigns, are largely unknown." Are these different or related processes? "The present situation in endemic treponematoses offers unusual possibilities for further [immunological] research into these aspects of what appears to be persistent seroreactivity and possibly a persisting agent." The problems are fundamental since they concern concepts of mutual adaptation of man and the agent, or elimination of the agent, as possible alternatives in the ultimate biological sense.

If we turn to epidemiological research in relation to the environment, it is known that isolation, primitive living and economic conditions, physiographic and meteorological factors, and above all poor personal and environmental hygiene, facilitate the transmission of endemic treponematoses. The importance of differences in personal hygiene, socio-economic status, and environmental practices, particularly with a religious background, in different groups of people living in the same geographical areas in relation to age prevalence of endemic treponematoses is shown in Fig. 7 for yaws in Thailand and for endemic syphilis in Bosnia. The data do not, of course, measure directly the influence of religious practices on the disease.

Environmental characteristics are unlikely to change rapidly in the rural areas of most developing countries. Presumably, they continue to support transmission at the lower levels of prevalence attained after mass penicillin campaigns. Little is known of the nature of the transmission process itself, for either yaws or endemic childhood syphilis. Apart from the data included in Fig. 7, the relative importance and mutual interactions of physical, biological, and other factors in the environment that
perpetuate natural infection and determine virulence are generally unknown. Studies of environmental factors and definitions of major factors could be of help in understanding the nature of persistent infections, and could possibly lead to the adoption of simple environmental measures to facilitate the control of such disease. Quantitative investigations of this type—based on incidence observations, in contrast to the prevalence studies discussed in this article—could probably be established in suitable endemic areas. The information obtained could also provide the foundations for a preliminary epidemiological model of yaws that is at present under consideration.

Some implications of surveillance for health administrations

"The findings in surveillance studies of endemic childhood treponematoses are of practical value for national health administrations. Continued surveillance brings out the long-term results of campaigns against these diseases, and shows whether the campaigns are effectively performed. Sero-epidemiological post-campaign surveys reveal changing patterns of disease and infection and furnish data on recrudescence, level of continued transmission, etc. A technical basis is thus provided for immediate measures that may be needed, and for determination of the emphasis required in further overall planning of communicable disease control by the health administration. Another result of mass campaigns that has public health implications is the increasing number of children in the generation born after the mass campaign who remain sero-negative when they reach puberty. The existence of significant cross-protective immunity between yaws and venereal syphilis and between pinta and venereal syphilis has recently been confirmed [Medina, unpublished data]. The increase in subjects susceptible to venereal syphilis in the new generation as a result of mass campaigns in rural areas where childhood treponematoses were formerly endemic is therefore a new epidemiological factor. In some areas, 60–70% of children reaching puberty are now susceptible to venereal syphilis, as against 5–10% 20 years ago. In conjunction with other recent ecological changes, this development must be expected to facilitate the spread of venereal adult treponematoses. Venereal syphilis has in fact been reported in rural areas of some countries where yaws was previously endemic [e.g., Western Samoa, Thailand, New Guinea]."

Information furnished by sero-immunological treponematoses surveillance studies contributes, together with similar data from other communicable disease studies, to assessments of the effectiveness of single- or multi-subject mobile health team activities in developing countries. The information is also helpful in appraisals of suitable timing for the integration of continuing control measures into developing basic health services; this involves the capacity of the basic services and the availability of trained personnel at any one time. Little factual information is available on these, and related, long-range problems in developing countries and inter-disciplinary long-term research is needed.
RÉSUMÉ

MÉTHODES DE SURVEILLANCE DES TRÉPONÉMATOSES ENDÉMIQUES ET INVESTIGATIONS SÉRO-IMMUNOLOGIQUES SUR LES MALADIES «EN VOIE DE DISPARITION»

Le traitement de collectivités entières par la pénicilline retard a entraîné à l'origine une très forte régression des tréponématoses endémiques, comme l'ont montré les enquêtes de contrôle menées parallèlement. Cependant, dans de vastes régions d'endémicité, les manifestations cliniques précoces du tps n'ont pas entièrement disparu. La syphilis endémique de l'enfance a pu être éliminée dans un cas où les conditions générales améliorantes étaient favorables. Dans la plupart des zones atteintes, la transmission de l'infection persiste, avec une intensité variable, comme l'attestent les résultats des investigations séro-immunologiques. On assiste périodiquement à des recrudescences de la maladie et à l'apparition de foyers localisés.

Des campagnes de pénicillinothérapie de masse ont été entreprises dans 46 pays; à la fin de 1970, quelque 160 millions de personnes avaient été examinées et près de 50 millions de cas, avérés ou latents, et de contacts avaient été traités. Depuis plusieurs années, on recourt aux enquêtes séro-immunologiques à long terme pour suivre les changements apportés par ces mesures aux aspects cliniques et épidémiologiques des tréponématoses et étudier certaines infections tréponématiques «en voie de disparition». On a été ainsi amené à des recherches fondamentales sur les mécanismes immunologiques responsables de la persistance de l'infection et de formes infectantes chez l'hôte. Les tréponématoses endémiques représentent à cet égard un secteur de recherche d'un intérêt exceptionnel.

Les enquêtes séro-immunologiques, surtout si elles sont à fins multiples, constituent une source permanente d'informations pour les administrations sanitaires nationales en matière de lutte contre les maladies transmissibles et de développement des services de santé de base.

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