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CLINICAL, SEROLOGICAL AND EPIDEMIOLOGICAL FEATURES OF FRAMBOESIA TROPICA (YAWS) AND ITS CONTROL IN RURAL COMMUNITIES*

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Introduction

In Scandinavian countries, as well as in other parts of the world, much has been said, and done, in recent years concerning health problems of developing countries. Little scientific information has come to light, however, concerning dermatological phenomena in the tropics as expressions of serious systemic disease—epidemic or endemic. *Framboesia tropica*—or yaws—(pian, buba) is an area where such knowledge has become available, and where also large-scale action has been taken through bilateral and international technical assistances programmes. Yaws has in fact offered itself as an opportunity to illustrate the increasingly needed integration of dermatology with epidemiology, immunology, methodological and other aspects, as part of specialised medical disciplines. There is a growing interest of Scandinavian doctors and students in such scientific approaches. "The clinical, serological and epidemiological features of yaws and its control in rural communities" has therefore been chosen as the topic for presentation at the 1968 "Sven Hellerström lecture".

Extent and Course of Yaws

(i) *Yaws* is one of three known human treponemal diseases of children in rural developing countries (Fig. 1). It is prevalent in humid regions in the tropical belt around the globe; (ii) *Pinta* is prevalent in some countries in Central and South America, and (iii) *Prepubescent syphilis*—also known as "endemic non-venereal syphilis of children" is usually encountered in arid, subtropical and adjacent zones in Eastern Mediterranean, African and Asian countries. In addition to these childhood treponematoses, the treponemal disease of adults—venereally transmitted syphilis—is ubiquitous and not identified directly in Fig. 1. The characteristics and relationships of the treponematoses as a group are summarised in Table 1. Attention is drawn particularly to the possible simian reservoir in yaws (in cynocephal African monkeys) and to cross-immunological aspects of yaws and venereal syphilis, which we shall have occasion to discuss later.

Tropical yaws is the most significant of the childhood treponematoses, with an estimated prevalence twenty years ago of more than 100 million cases among the approximately 400 million people living in affected rural areas of Africa, the Americas, South East Asia and the Western Pacific regions. In 1968 it is estimated that some 50 million continue to live at risk of infection.

The causative organism of yaws, *T. pertenue*, is transmitted by direct bodily contact between children, usually via the hands—which are the most active human "instruments" at early ages (12). Skin traumas, warm temperatures and humidity facilitate transmission and body entry in the non-hygienic conditions of developing countries. In its *clinical* natural course, yaws is characterised by initial lesions in children, fol-

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Table 1. *Epidemiological and other relationships of the treponematoses*

	Yaws	"Endemic" syphilis	Pinta	Venereal syphillis
Organism:	T. pertenue	T. pallidum II	T. carateum	T. Pallidum I
Incubation:	3–4 weeks or more	?	?	2–8 weeks
Transmission:				
Direct (person to person)				
Venereal	No	No	Not described	Common
Non-venereal	Commonly child-to-child	Commonly child-to-child, Ceremonial kissing	Usual	Rare
Indirect				
Communal utensils	Possible?	Drinking vessels	Not described	Unusual
Hands of children	Probably frequent	Possibly frequent	?	No
Congenital	No	No	No	Occasional
Sources of treponemes:	Skin surface, anywhere	Buccal mucous membrane and skin lesions	Skin surface, anywhere	Genital, skin and mucous membrane lesions
Infectiousness of lesions:	Perhaps a year	Many months	Many years	Some months
Extent of infectious lesional surface:	Large	Small	Very large	Small
Reservoir of infection:	*Children*, 4–15 years; contacts in home, school and village; latent cases; "silent" simian reservoir	*Children*, 2–10 years; household contacts; latent cases	*Ages* 10–30. Long-standing surface lesions	*Adults*, prostitutes—amateur and professional; promiscuous females, and homosexual and heterosexual males, seafarers, armed forces, latent cases etc.
Immunology: Cross-protective immunity	Between yaws and— "endemic" syph.: Unknown; pinta: No; venereal syph.: Relative	Between "endemic" syph. and— yaws: Unknown; pinta: Unknown; venereal syph.: Relative?	Between pinta and— yaws: Relative; "endemic" syph.: Unknown; venereal syph.: Relative	Between venereal syph. and— yaws: Relative; "endemic" syph.: Relative; pinta: Relative
Serological tests:	Flocculating, complement fixing reagins, immuno-fluorescent and immobilising treponemal antibodies	Serological cross-reactivity in all tests	Serological cross-reactivity in all tests	Serological cross-reactivity in all tests
Therapy:	Adequate penicillin therapy, preferably longacting PAM or DBED resulting in several weeks treponemicidal blood/tissue level	Same	Same	Same

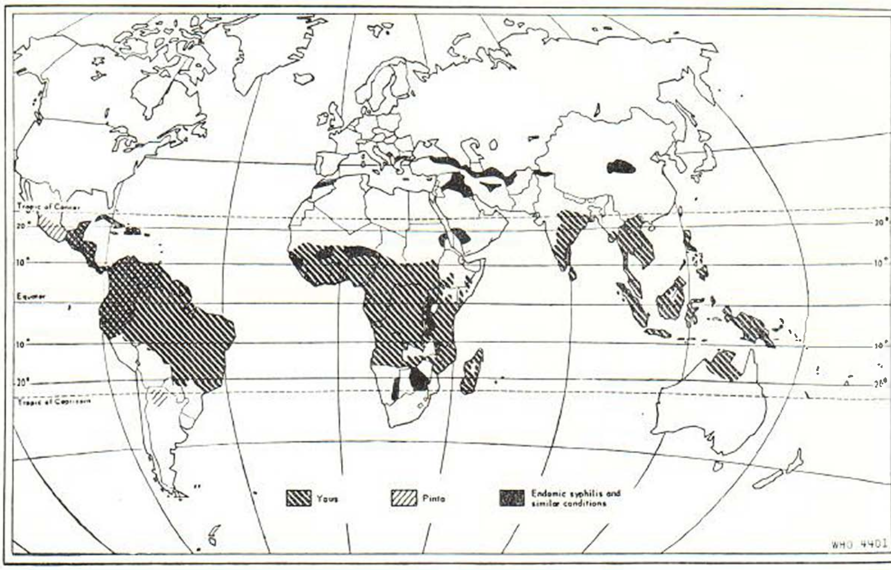


Fig. 1. Geographical distribution of the endemic treponematoses of childhood.

lowed by crops of infectious, relapsing skin eruptions (Fig. 2). In adolescence and in later life, outbreaks of hyperkeratoses of palms and soles occur (Figs. 3 and 4). Life-long invaliding sequale (Fig. 5) or destructive lesions of the skin, the subcutaneous tissues and bones may follow (Figs. 6 and 7). From a human, economic and social viewpoint, it is important to note that some 10 % of those infected with yaws would eventually become invalids from late lesions in the natural, untreated course of this chronic infection. There is no evidence, however, of the occurrence of congenital yaws or of late manifestations in the form of cardiovascular or neurological involvement, such as occur in venereal syphilis.

In systematically examined tropical rural communities we have encountered as much as 20–30 % active clinical lesions, of which 2–3 % were infectious, and with 60–70 % of the population showing serological evidence of past or present infection with *T. pertenue* (*e.g.* former Netherlands New Guinea). In a yaws community most infections are of long duration. On treatment, seroreversal will, therefore, occur in a very small percentage of cases only. So-called "burnt-out" cases are relatively rare. When we also take into account the relapsing tendency of latent cases, the immunological aspects become important, particularly when the immediate clinical reservoir of the disease is rapidly reduced as a result of mass penicillin campaigns. We will return to these immunological aspects after first appraising some general features of mass campaigns against yaws.

Yaws Mass Campaigns

Mass campaigns were already attempted in many tropical areas when therapy of yaws depended on multiple injections of arsenicals and/or bismuth. Treatment surveys and resurveys based on clinical inspection were undertaken in community-wide projects in Western Pacific islands as early as 1923 and subsequent years (3, 19). However, the epidemiological concept that treatment was necessary also of symptomless household contacts and presumed latent cases in addition to manifest clinical disease had as yet not evolved. Neither were demographic and census aspects taken adequately into account in relation to the survey coverage obtained, *etc.* These quantitative aspects are held essential today. From the accounts of the early yaws mass campaigns, it is clear that the attempted multi-

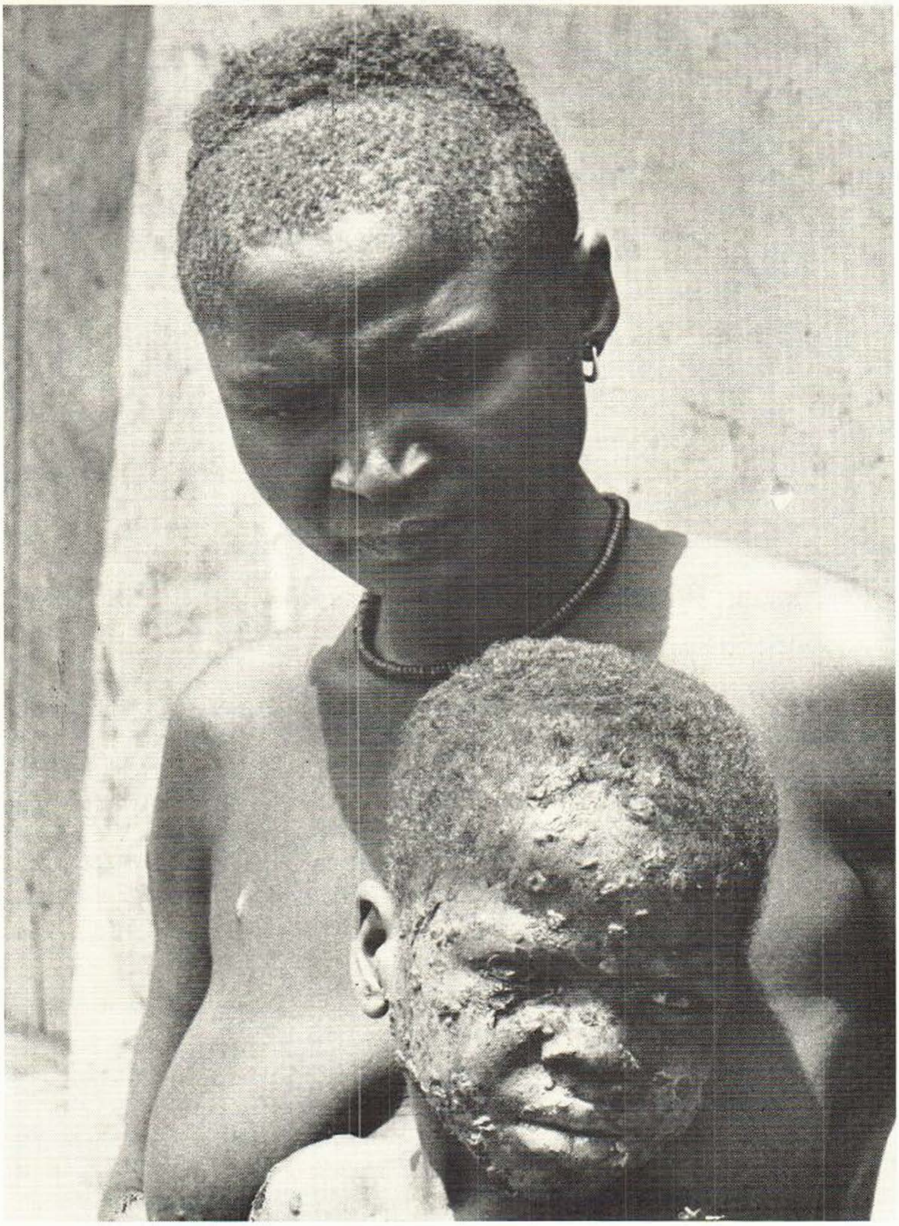


Fig. 2. Outbreak of early yaws in a five year old Nigerian boy. Papular, crusty, infectious lesions of the face.

injection procedure with arsenicals and/or bismuth suppressed the surface lesions of early yaws, but that treatment could usually not be completed under primitive field conditions. Disappearance of the early lesions was interpreted by the rural population as disappearance of the disease itself. It was followed by the disappearance also of the interest of the public and health administrations in consolidating the initial results by post-campaign measures. Recurrence of yaws took place within a few years of all early attempted programmes. From a long-range viewpoint, these campaigns must therefore be considered as having been of transient palliative public health value, although their "Hippocratic" effect on large numbers of children and

Fig. 3. Mild, early palmar hyperkeratosis of yaws; painful and interferes with work.

Fig. 4. Plantar hyperkeratosis occurring in early or late stages of yaws, leaving scarring and pigmentation. Early lesions arise from epidermal changes leading to death and disintegration of superficial cells which are resulting in the tissue loss seen.

adults in rural tropical areas at the time cannot be doubted.

The introduction and use of long-acting penicillin in the combating of the endemic treponematoses of childhood after 1948, notably the so-called *PAM* (procaine penicillin G in oil with aluminium monostearate) *DBED* (dibenzylethylenediamine penicillin G/or benzathine penicillin) allowed single-session therapy to be used on *clinical indication* and contact treatment to be applied on *epidemiological indication*. These long-acting preparations gave treponemicidal penicillin blood and tissue levels which exceeded the 2–3 weeks' incubation period of yaws (and other treponemal diseases). The clinical effectiveness was striking (Figs. 8–13). These developments rapidically improved the public health scope possible in developing countries in the combating of yaws (as well as the other endemic treponematoses of childhood—pinta and "endemic" syphilis).

In 1949 the World Health Organization accepted an epidemiological rather than the previous more limited clinical outlook on the treponematoses, and this set the scene for a technical assistance programme of mass treatment campaigns against yaws, and the other endemic treponematoses (25). This programme has since gone forward. Its objectives include control of dis-

Fig. 5. General anterior bowing of both tibias due to active bone lesions in a child, leaving inactive sequelae, "Sabre Tibia".

ease, evaluation of mass campaign results and long-term sero-epidemiological surveillance, three aspects with which this presentation is notably concerned. The strengthening of rural health services and training of personnel were also part of the programme, but are only marginally mentioned in this presentation.

Up to 1966 some 155 million people in 45 countries had been examined in this international programme and some 47 million clinical cases, latent cases and contacts had been treated with penicillin (Table 2). The national and international costs of the programme approximated 50 million dollars. The role of the United Nations Children's Fund (UNICEF) is notable in regard to its material support. The programme itself was kept under technical review by WHO Expert Committees (26, 27, 29), international conferences and symposia on yaws (2, 16, 28), Scientific Study Groups on Treponematoses Research (30) and on the Integration of Mass Campaigns into General Health Services (31), etc.

A remarkable fall in endemic treponema-

Fig. 6. Active late ulcerations of skin and subcutaneous tissues of the face which leave scars and pigmentation changes.

Fig. 7. Healing destructive, late ulceration of facial yaws (gangosa). Late ulcerations also occur about joints and cause marked disability (contractures).

toses took place after 1949–1950. By way of illustration Table 3 a evaluates the outcome of the mass campaign in 15 provinces in North East Thailand, comparing findings at Initial Treatment Surveys (ITS) and the so-called Last Re-survey before Consolidation (RSL). Table 3 b shows these findings on a percentage basis. The enormous reduction in cases of yaws and the public health benefits are obvious in terms of infectious as well as total yaws. It is noted that mass campaigns are in their early stages based on clinical observations alone since millions of people cannot in this type of campaigns be examined serologically in developing countries, but small serological

Table 2. *Endemic treponematoses of childhood. Persons examined and treated in the context of the International treponematoses programme of WHO, 1950–1966*

Region	Persons examinated at initial treatment surveys	Examinations at all surveys and resurveys	Cases, contacts and latents treated
Africa[1]	27,269,000	79,120,800	19,780,000
America[1, 2]	8,340,000	11,205,000	6,110,000
E. Mediterranean[3]	758,000	1,860,100	324,500
Europe[3]	145,000	883,500	52,500
S.E. Asia[1] W. Pacific[1]	117,515,000	274,971,000	20,850,000
Total	154,027,000	368,040,400	47,117,000

[1] Yaws.
[2] Pinta.
[3] Endemic non-venereal syphilis ("bejel", "dichuchwa", *etc.*).

Table 3 a. *Population and yaws cases at Initial Treatment Surveys (ITS) and last resurveys before consolidation (RSL)*[1] *or school "checking" surveys (Sch.RS). Provinces in North-East Thailand 1952–60*[2]

Initial Treatment Survey (ITS)				Last Resurvey before consolidation (RSL)		
Population	People examined	Yaws cases	Survey areas	Population	People examined	Yaws cases
409,424	376,544	28,845	I	403,221	320,768	2010
441,668	381,817	27,709	II	511,554	470,802	11,554
333,067	303,046	19,362	III	94,126	80,905	1949
340,690	307,669	8531	IV	37,272	26,946	9
636,830	573,379	33,123	V	190,761	173,192	1880
135,044	123,027	1731	VI	17,771	14,727	163
385,005	313,338	24,440	VII	402,752	353,796	9907
319,268	295,250	7120	VIII	—	—	—
153,126	136,411	4989	IX	69,443	62,017	709
554,623	522,324	17,916	X	191,162	169,240	1446
440,419	365,603	46,942	XI	326,133	236,745	2712
289,264	264,143	3269	XII	—	—	—
471,874	336,538	3419	XIII	287,965	241,074	1877
605,325	538,727	47,836	XIV	437,559	336,462	2197
445,845	387,158	20,749	XV	266,412	244,812	2828

[1] There were several surveys between ITS and RSL.
[2] Returns from TCP Thailand to WHO. Project Director: Dr Somboon Vacharotai.

pilot areas were established for study purposes in different areas—a feature to which I shall have occasion to refer later.

From the photographs already shown (Figs. 8–13) we have seen the clinical effectiveness of long-acting penicillin in individual cases of early infectious yaws. Penicillin acts well also on other active yaws, and late cases can to a large extent be arrested. This gives rise to an overall community effect on the disease, with different clinical regression patterns which are of interest. A number of such patterns are possible (15, 17, 18, 24). In Table 4 are grouped clinical patterns of active yaws in children (below 15 years) and in adults (above 15 years), as observed in 13 WHO pilot studies in hyperendemic, meso-en-

Table 3 b. *Percentage people examined an prevalence of total and infectious yaws at surveys[1] etc. based on preceding table. Provinces in North-East Thailand 1952–60[2]*

Percentages					
People examined		Yaws cases			
		ITS		RSL or Sch.RS	
ITS	RSL or Sch.RS	Total	Infectious	Total	Infectious
91.9	59.0	7.93	1.06	0.6	0.08
86.4	83.6	7.25	1.47	2.5	0.26
90.9	82.6	6.39	0.21	0.30	0.03
90.3	72.3	2.77	0.31	0.03	0.01
90.0	90.8	5.78	0.04	1.08	0.03
91.1	82.9	1.61	0.01	1.12	0.02
81.4	89.7	7.8	1.20	1.41	0.01
92.5	—	2.41	0.03	—	—
89.1	89.3	3.66	0.04	1.14	0.01
94.2	88.5	3.42	0.31	0.85	0.04
83.0	46	8.8	1.34	1.15	0.11
91.3	—	1.25	0.02	—	—
71.3	44	1.01	0.21	0.3	0.06
88.9	34	8.88	1.68	0.7	0.01
86.8	91.9	5.61	0.47	1.16	0.01

[1] There were several surveys between ITS and RSL.
[2] Returns from TCP Thailand to WHO. Project Director: Dr Somboon Vacharotai.

demic, hypo-endemic and feeble prevalence areas at the beginning of mass campaigns. Long-acting penicillin provides a momentum for very rapid transition from one clinical disease pattern to another. This is illustrated in some detail in Western Samoa (Table 5). The extremely rapid regression of infectious yaws and of active clinical yaws as a whole is evident already after the first and second resurveys, that is, within a period of 1–2 years. The population coverage was high in the mass campaign surveys and resurveys. Representative survey designs were used in the two last sampling surveys. We should note that in spite of the immediate—and impressive—community results obtained, occasional active cases continue to occur, providing *dermatological* and other *clinical* evidence that transmission of infection has continued at a low level.

Sero-epidemiological Surveillance Studies

We will now return to the immunological features which characterise yaws. Flocculating and complement-fixing lipoidal antibodies, as well as fluorescent, and immobilising treponemal antibodies, are produced by the host in response to infection with *T. pertenue,* in much the same way as in syphilis and pinta. The same serological tests are used (*e.g.* VDRL, WR, FTA, TPI) in immunological studies. No routinely useful serological test is available to differentiate between yaws and syphilis (or pinta). No differences have been elicited by the cross-use of *T. pallidum* or *T. pertenue* as antigens in the FTA or TPI tests in syphilis or in yaws. It is, however, possible in scientific experimentation, to differentiate between these treponemal infections in certain laboratory animals (*e.g.* the golden hamster).

Let us then consider the immunological age profile for different endemicity of yaws before and after penicillin mass campaigns based on lipoidal antigen testing—VDRL—(Fig. 14). The patterns of former Netherlands New Guinea, Western Samoa and New Hebrides, *etc.* indicate the very rapid age "saturation" with seroreactors

Fig. 8. Administration of PAM to child shown in Fig. 2.—under mass campaign field conditions.—Generalized eruption on trunk, arms and limbs seen.

from early childhood in hyperendemic areas. Already at the age of approximately five years a 40 percent saturation level of seroreactors is obtained, while this level is reached at somewhat later ages in meso-endemic Cambodia and at still later ages in the hypo-endemic Tonga Islands. (It is obvious that lower saturation levels and at different ages can also be used as indices.) The catalytic curve characteristic of hyper-

Fig. 9. Same child as in Figs. 2 and 8 showing the generalized eruption of waning papular, infectious early yaws affecting face, trunk and limbs, a few days after PAM therapy.

endemic areas (reagin reactors in VDRL) is in contrast with the sigmoid-shaped curve, with relatively low seroreactor rates in the treated study areas of Eastern Nigeria and Thailand. The three profiles from these latter areas were established in sero-epidemiological surveillance studies approximately 10 years after the initial treatment surveys of the mass campaigns. The post-mass campaign evaluation and re-

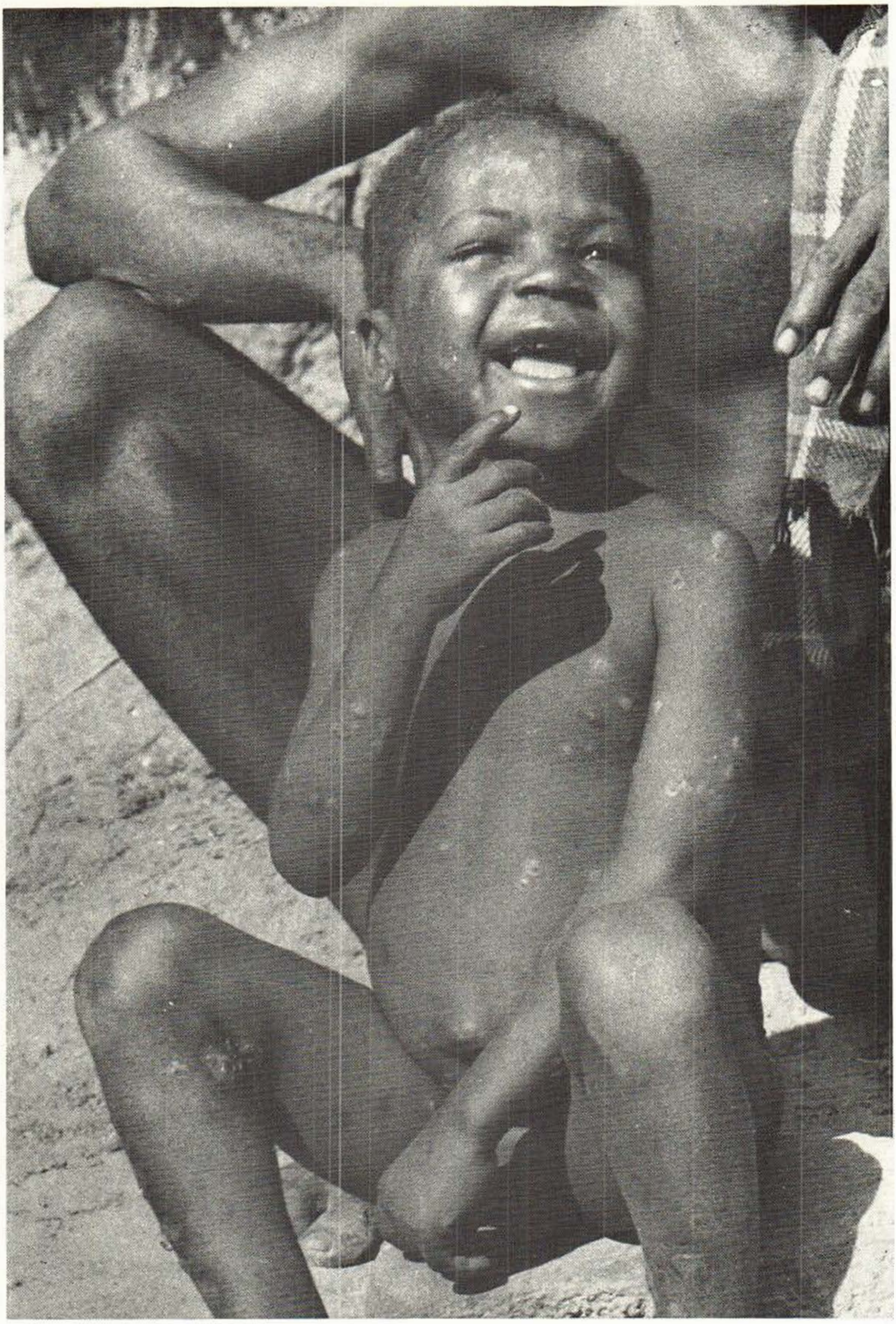


Fig. 10. Yaws lesions disappearing and obvious healing. Child realizes improvement.

search projects undertaken in this way in the surveillance of yaws by our group since 1960 are based on dermatological and other clinical investigations as well as on serological examinations and have been summarised in Tables 6 a and 6 b. From Table 6 a it will be seen that only in Northern Nigeria and Western Samoa was the mass campaign coverage of the population epidemiologically satisfactory at initial treat-

Fig. 11. Near-complete healing of lesions after two weeks. Complete healing will result within next two weeks or so.

ment surveys (ITS). Nevertheless, the regression of infectious yaws is evident in all four instances. In Table 6 b the population coverage is unsatisfactory at ITS in all four instances, but also here the regression of infectious yaws is evident from these post-campaign surveillance studies. Sero-prevalences attained by VDRL are variable, but have remained high in some areas of initial low prevalence of infectious yaws, *e.g.*

Fig. 12. Typical papillomatosis eruption of early yaws, highly infectious, and may last for 6 months. Annular papilloma on right cheek.

North East Thailand and Mid-western Nigeria. (The large serum collections established for purposes of yaws investigations have also been utilised for multi-subject exploitation and study of several other conditions. The nature of these activities and the laboratories concerned in this international collaborative programme have been included in Tables 6 a and 6 b.)

In sero-epidemiological studies of this kind—undertaken for the first time in yaws in rural tropical countries—several questions arise. *First,* one would like to know something about the representativeness of the sampled population. In the methodology developed, the clinical data and serum

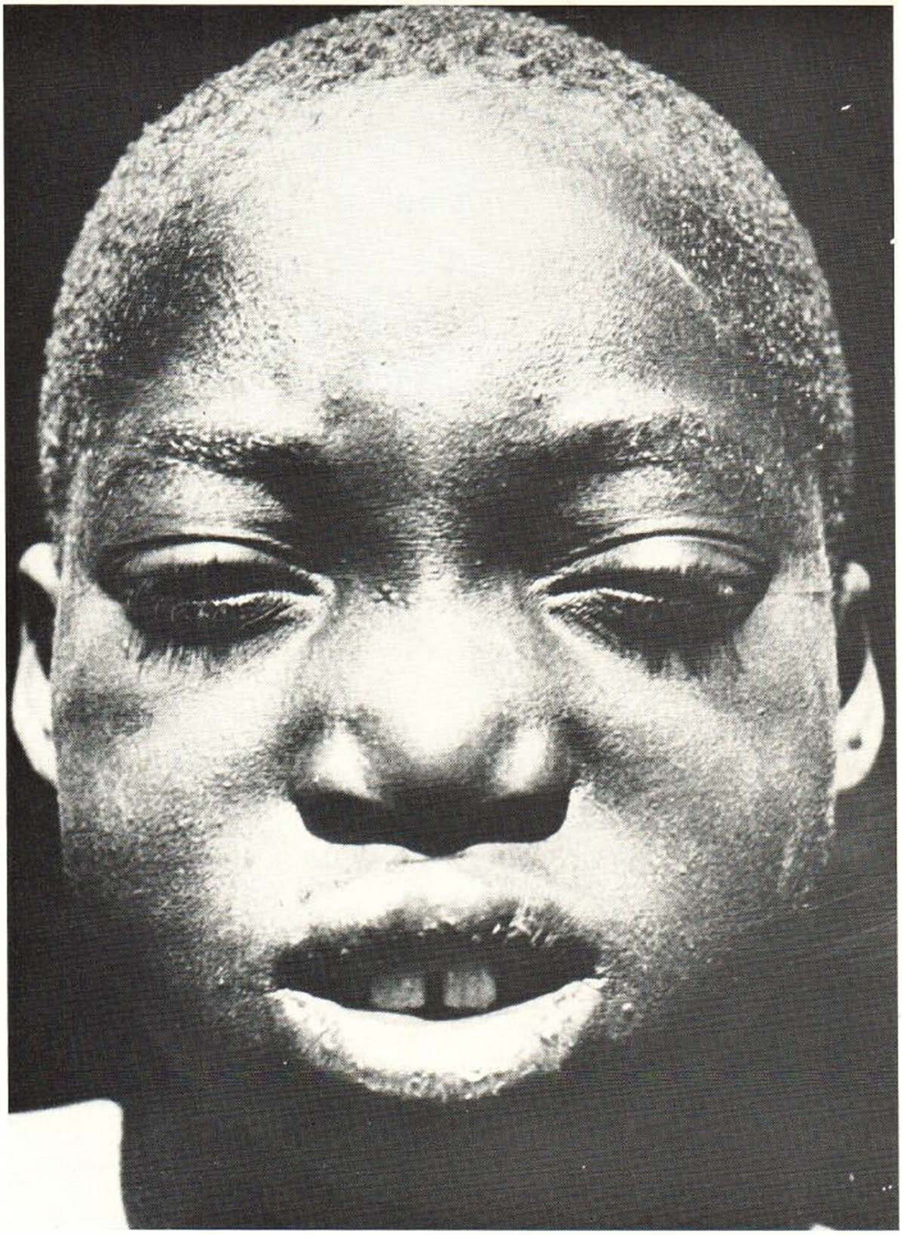


Fig. 13. Patient in previous photograph after treatment. No scars from papillomatous lesions.

collections are obtained, based on predetermined, stratified, statistical survey designs. The sampling units are rural villages and households with adults and children being examined in groups representative of the distribution of the population. Some 50–60 sampling points may be covered in these self-contained, internationally staffed projects, which are of 2–3 years' duration and take place 10–15 years after the penicillin mass campaigns. *Secondly*, one would like to know how faithfully the field performance actually reflects the theoretical sampling design established in advance. To elucidate this we have compared the survey design requirements with the actual cover-

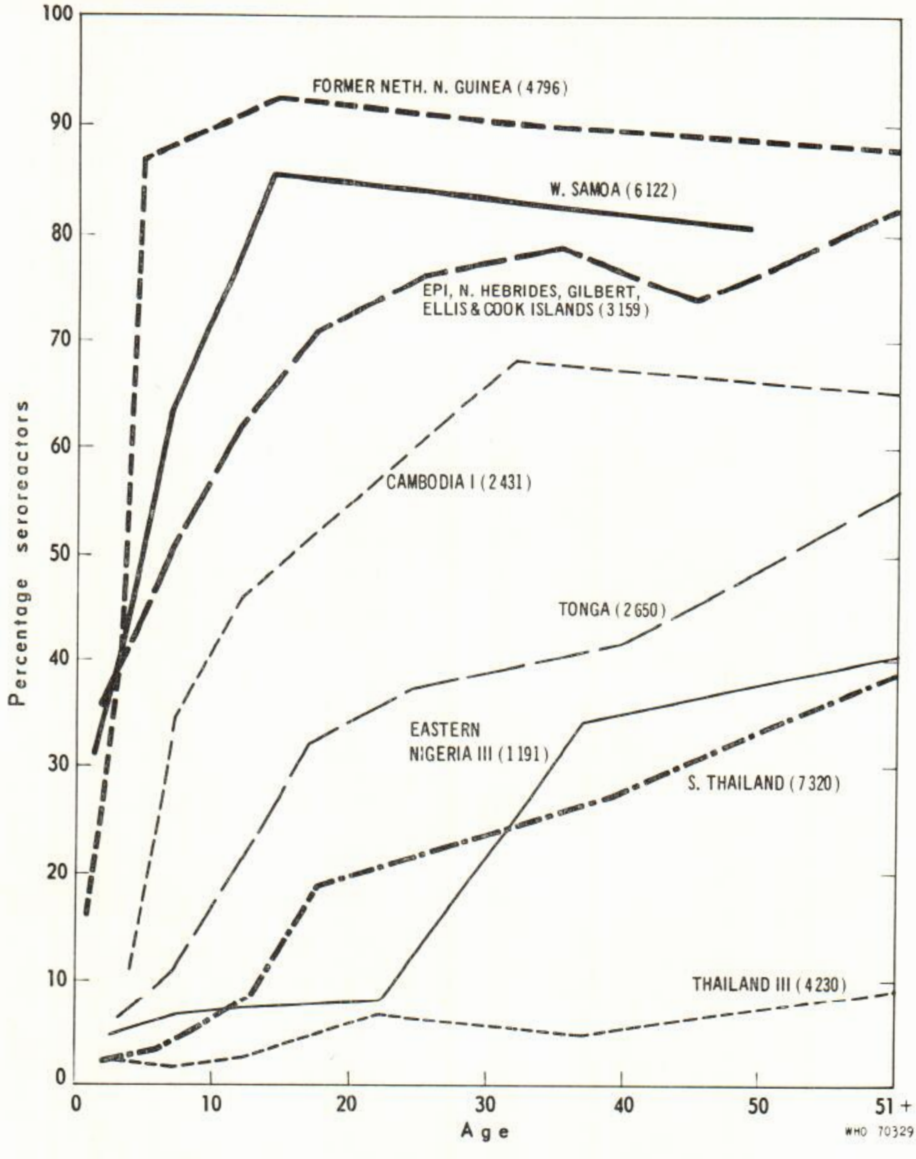


Fig. 14. Serological patterns of yaws in WHO study areas. Sero prevalence (VDRL) by age.

ages obtained in the clinical and serological field sample examinations in Northern Nigeria (Table 7). The requirements were: 100 % of the registered children and adults in each sample should be examined clinically; one-third of the children and one-fifth of the clinically examined adults should be serologically tested in a sub-sample. Several points emerge from Table 7: (a) the coverage of the clinical sample was good, (b) the serological sampling was also good, but it would not have been possible to obtain adequate coverage of the serological sub-sample in the children without the use of the fingerprick dried blood technique for FTA testing ("rondelles") to supplement venipuncture—a point which we will discuss later—and (c) the fraction of adults examined by serological tests was in quite good agreement with the design.

Table 4. *Clinical age patterns of active yaws at initial treatment surveys (ITS) in WHO study areas of different endemicity 1951–1956*

Pilot areas	No. examinated	−15 years		+15 years		Total active yaws		Endemicity level
		Infectious %	Non-infectious %	Infectious %	Non-infectious %	No.	%	
New Hebrides	868	12.9	1.4	6.2	6.3	229	26.4	Hyper-endemic > 10 % active yaws
Western Samoa	4309	3.7	6.9	0.7	11.4	977	22.7	
Former Netherland N. Guinea	731	1.9	1.8	1.5	17.0	163	22.3	
British Solomon Islands	3623	3.8	3.2	1.6	11.8	738	20.4	
Upper Volta	1193	1.8	3.1	0.9	12.9	223	18.7	
Total	10,724	4.1	4.4	1.5	11.6	2330	21.7	
Cambodia	6638	1.2	0.8	0.1	6.2	551	8.3	Meso-endemic 5–10 % active yaws
Thailand (P)	9292	1.0	1.24	0.05	3.0	491	5.3	
Total	15,930	1.1	1.1	0.07	4.3	1042	6.4	
Sierra Leone	6501	0.18	0.45	0.08	3.54	275	4.2	Hypo-endemic 1–5 % active yaws
Cambodia II	4699	0.08	0.08	0.02	2.10	106	2.3	
Tonga	5199	0.06	0.13	0.02	1.80	106	2.0	
Total	16,399	0.21	0.23	0.04	2.6	487	3.0	
Malayasia	7068	0.4	0.20	0	0.01	43	0.6	Feeble prevalence < 1 % active yaws
S. Thailand	7320	0.16	0.04	0.01	0.05	18	0.26	
Togo S/M	5019	0	0	0	0.02	1	0	
Total	19,407	0.10	0.08	0.005	0.003	62	0.32	

Table 5. *Yaws control in the WHO Western Pacific Region. Western Samoa 1955/56–1965/66*[1]

Type of survey	ITS	1/RS	2/RS	3/RS	4/RS	5/RS	6/RS[2]	ESRS[3]
Year	1955/56	1956	1957	1958	1959	1960	1961	1965/66
Estimated population	96,969	96,969	100,174	102,180	103,000	108,750	110,000	113,000
Population examined	93,767	59,761	99,736	97,000	98,470	100,446	28,820	10,220
%	96.7	61.6	99.6	94.6	95.6	92.4	26.2	9.0
Active yaws	10,356	38	36	12	11	5	8	1
%	11.04	0.06	0.04	0.01	0.01	0.005	0.03	0.001
Infectious yaws	2767	13	28	12	11	5	8	0
%	2.95	0.02	0.03	0.01	0.01	0.005	0.03	0.00
Non-infectious yaws	7589	25	8	0	0	0	0	1
%	8.09	0.04	0.01	0.00	0.00	0.00	0.00	0.001

ITS: Initial Treatment Survey; 1/RS: First Resurvey; 2/RS: Second Resurvey, *etc.*
[1] WHO Medical Officers: Dr F. Tross, Dr W. Fröhlich and Dr P. N. Wang.
[2] Only children under 15 years examined (6/RS).
[3] Epidemiological serological (ESRS) random sampling survey.

Table 6 a. *WHO epidemiological surveillance of yaws. Sero-epidemiological evaluation and research surveys following mass campaigns, 1960–67. Stratified random designs, multisubject exploitation of serum collections*

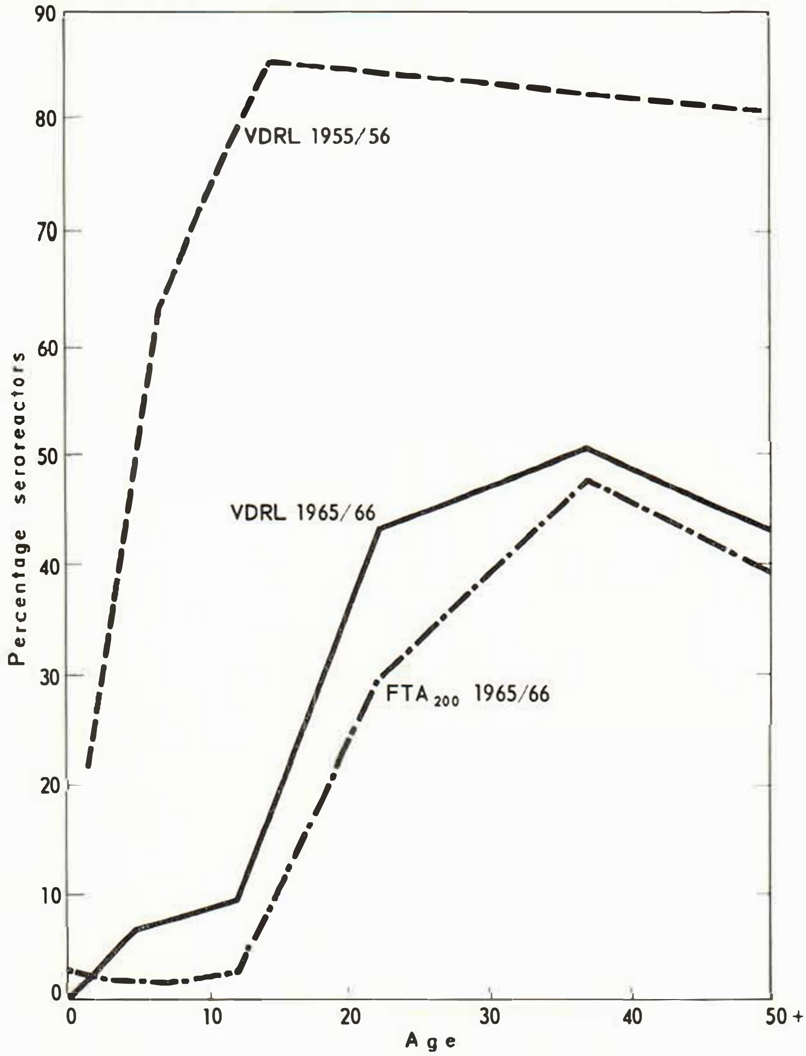
Country	Mass campaigns					Epidemiological serological surveys and investigations											
		Rural census population millions	Examined at ITS[1]		Inf. Yaws %	Year	Inf, Yaws %	Examined		Sero-reactors %	Sampling fraction points		Efficiency Coverage %	Treponematoses		Multisubject exploitation of material	
			millions	%				Clinical no.	Serological no.		%	No.		WHO Laboratory	WHO Reference Centre	Other conditons	Co-operating laboratories
Northern Nigeria (yaws)	1954–1956	2.5	2.2	88.9	4.2	1965–1966	0.01	7621	3802	21.7	0.34	48	95.3	Field Lab.	Institut Fournier, Paris	Arbovirus Malaria Immuno-haematology Others	Yale Arboviruses Lab., Newhaven Nuffield Inst. Med. Research, London International Haemaglobin Centre, London Centre Trans. Sanguine, Rouen
Togo (yaws)	1956–1961	1.5	0.6	40.0	4.1	1961–1965	0.11	16,171	7617	21.9	1.24	22	96.3	Field Lab.	Institut Fournier, Paris	Pertussis Parapertussis Poliomyelitis Measles Rubella Arbovirus	Institute of Epidemiology and Microbiology, Prague Institut Pasteur, Dakar
W. Samoa (yaws)	1955–1956	0.10	0.09	93.	3.0	1965–1966	0	7839	2788	16.2	6.35	32	97.3	Field Lab.	Laboratoires de Biologie Médicale, Paris	Helminthiasis Mycosis Eye conditions	—
Eastern Nigeria	1954–1955	6.8	3.6	54.4	1.9	1963–1964	0.07	8824	4201	22.6	0.14	56	91.9	Field Lab.	State Serum Inst., Copenhagen	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda

[1] ITS—Initial Treatment Survey.

Table 6 b. *WHO epidemiological surveillance of yaws. Sero-epidemiological evaluation and research surveys following mass campaigns, 1960–67. Stratified random designs, multisubject exploitation of serum collections*

Country	Mass campaigns					Epidemiological serological surveys and investigations											
	Year	Rural census population millions	Examined at ITS[1]		Inf. yaws %	Year	Inf. Yaws %	Examined: Clinical no.	Examined: Serological no.	Sero-reactors %	Sampling fraction %	Sampling points no.	Efficiency coverage %	Treponematoses: WHO Laboratory	Treponematoses: WHO Reference Centre	Multisubject exploitation of material: Other conditions	Multisubject exploitation of material: Co-operating laboratories
Western and Mid-west Nigeria (yaws)	1953–1955	4.2	2.1	50.0	1.8	1966–1967	0.2[2]	2991[2]	1329[2]	9.4 56.3	0.34	15[2]	92.4[2]	Field Lab.	VD Reference Laboratory, London	Malaria Arbovirus Others	Institute of Epidemiology, Prague Nuffield Inst. Med. Research, London Institut Pasteur, Dakar
South Thailand (yaws)	1953–1955	3.0	2.1	70.0	0.13	1961–1962	0.06	15,538	7320	23.2	0.49	16	87.3	Field Lab.	State Serum Inst., Copenhagen	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda
Philippines (yaws)	1952–1954	2.4	0.8	33.3	0.10	1962–1963	0.04	16,024	8001	13.1	0.67	37	90.2	Field Lab.	State Serum Inst., Copenhagen	Rubella Measles Mumps Poliomyelitis Ambiasis Bilharzia Vaccinia Arbovirus	Yale Arboviruses Lab., Newhaven National Institutes of Health, Bethesda
N. E. Thailand (yaws)	1952–1954	8.4	4.2	50.0	0.7	1960–1961	0.11	22,744	11,935	32.2	0.25	24	91.4	Field Lab.	State Serum Inst., Copenhagen	Pertussis Parapertussis Poliomyelitis Measles Rubella	Institute of Epidemiology and Microbiology, Prague National Institutes of Health, Bethesda

[1] ITS—Initial Treatment Survey. [2] Mid-west Region only.



Age	1955-56		1965/1966				
	VDRL		VDRL			FTA 200	
	Examined	Reactive %	Examined	Reactive %	≥ 16 dil	Examined	Reactive %
Children	2 559	53.1	1 992	7.1	0.6	3320	1.7
Adults	3 563	82.1	796	39.1	1.6	915	37.3
All ages	6 122	69.9	2788	16.2	0.9	4245	9.1

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Fig. 15. Serological age patterns in yaws, W. Samoa at initial treatment survey and ten years later WHO Project Laboratory, W. Samoa: Drs. W. Frolich & P. N. Wang.

Thus the field performance was generally acceptable and close to the theoretical survey design. *Thirdly,* one would like to appraise the actual long-term immunological effect of mass campaigns in a given population in relation to time. To illustrate this we have chosen Western Samoa (Fig. 15), where we already showed the clinical regression pattern in repeated investigations over a ten-year period (1955/56 to

Table 7. *Sero-epidemiological surveillance of yaws, Northern Nigeria 1965/66.*[1] *Actual field examination coverage and the selected sample. Both strata, 48 sampling points*

AGE	Registered accord. to survey design	Clinical sample			Serological sub-sample		Rondelle sub-sample	
		Absent	Examined	%	Examined	%	Examined	%
-1	349	11	338	96.8	—	—	—	—
1–4	1273	41	1232	96.8	309	25.1	1190	96.6
5–9	1285	83	1202	93.5	380	31.6	1190	99.0
10–14	580	60	520	89.7	159	30.6	514	98.8
Children	3487	195	3292	94.4	848	28.7[2]	2894	98.0[2]
15–29	2246	172	2074	92.3	426	20.5	433	20.9
30–44	1425	114	1311	92.0	286	21.8	291	22.2
45–59	626	35	591	94.4	129	21.8	130	22.0
60+	374	22	352	94.1	63	17.9	63	17.9
Adults	4671	343	4328	92.7	904	20.9	917	21.2
Unknown	60	59	1	1.7	—	—	—	—
Total	8218	597	7621	92.7	1752	—	3811	—

[1] WHO medical officers: Drs. G. Antal and F. Vorst. Serologist: J. D'Costa, Field officer: J. Maxwell.
[2] Computed on the number of children in age group 1–14 years.

1965/66—see Table 5). We note the original hyper-endemic immunological age profile (VDRL) when the mass campaign was initiated in 1955/56). Ten years later the sigmoid curve pervails, with a very low prevalence of VDRL reactors in the new child population, namely 7.1 percent as compared to 53.1 percent ten years previously.

It is well known that reagin tests are not specific in treponematoses, particularly in tropical areas, where frequent intercurrent infections and infestations as well as biological factors can interfere significantly. Methodological aspects like temperature, humidity, short-life of reagents, etc. also play a role. We have in fact found up to one-third false positive VDRL seroreactors in some tropical countries when using TPI as a reference test. While the factors concerned in false reagin positivity are proportionately of little importance in studies of yaws in hyper-endemic and meso-endemic areas, more refined methods are required to gauge a shrinking problem at progressively lower levels of prevalence. Use of more specific tests, notably the FTA and TPI tests, is then needed. In the case of Western Samoa, FTA was introduced in the surveillance study in 1965/66 (see Fig. 15) and the importance of "false" positive reagin seroreactors now shows up, particularly in the child age groups. But even so a certain proportion of children have fluorescent treponemal antibodies. Transmission of *T. pertenue* has thus not quite—but almost—ceased in the generation of children born since the beginning of the mass campaign. In addition to the clinical evidence (see Table 5) there is also immunological evidence that it has not been possible to "eradicate" yaws in Western Samoa over a ten-year period. From Fig. 15 we also see the slow but important serological recession in adults from some 80 percent in 1955/56 to some 40 percent ten years later, reflecting the tardive therapeutic effect of long-acting penicillin in the community.

Some Serological Problems in Tropical Countries

Mention has been made already of "false" reagin seroreactors in tropical countries. There are also other problems of direct, practical nature. Unfavourable time/temperature exposures (or variations of same) are known to result in denaturation of serum proteins, cause hemolysis and promote specimen contamination. Recently important differences have been evoked in regard to medium range temperature tolerance of reagins, immunofluorescent and immobilising antibodies, notably shown by Hederstedt in Sweden (14) and Vaisman in France (22). Moreover, significantly different results of VDRL testing at $+4$, $+20$ and $+37°C$ have been demonstrated in the laboratory under controlled conditions (5).

Long-distance transport of serum collections have often bedevilled serological surveys in the tropics in the past, in spite of the use of thermo-containers with natural ice at $+4°C$ or dried ice containers at $-70°C$. However, like most biological material, serum proteins remain unchanged by ultra-rapid freezing to extreme temperatures by use of liquid gases, such as is now obtainable with liquid helium or nitrogen at $-200°C$ or lower. In this context we have adapted bull sperm preservation in liquid nitrogen at $-200°C$ to the freezing of serum in the field in tropical countries and to long-distance shipment of large specimen collections for reagin and treponemal antibody examination at competent laboratories (10, 11).

A simple technique has also been developed, using dried fingerprick blood absorbed by blotting paper discs ("rondelles") for FTA testing of the eluent (23). This procedure is, within defined limits, practical in children and other individuals where venipuncture is difficult to achieve. We have used this technique as a supplementary method in our sero-epidemiological studies in the surveillance of yaws following mass campaigns, as already pointed out. The FTA dried blood eluent results compare well with the homologous serum FTA results in rural community studies of yaws. In Fig. 16 age-specific immunological profiles in a two-strata sampling survey in Northern Nigeria are shown. (i) We note first the close correlation between the FTA rondelle and FTA serum results in both strata. (ii) We also observe in both strata a slightly lower, but reasonable fit to the curve of the specific reference test—TPI. (iii) Finally, we note the prevailing upper position of the VDRL curve in both strata, reflecting the false positive reagin results by the VDRL test.

The "Last" Cases of Yaws

In communities where yaws is in rapid clinical regression, much attention has been focused on the so-called "last" cases—or residual clinical cases which continue to occur following mass campaigns against yaws. (i) Missed infectious as well as non-infectious clinical cases may obviously become direct sources of new infections in the community. (ii) In addition, early and late latent yaws without clinical signs may relapse and indirectly give rise to further infectious and non-infectious "last cases". These will require time to appear in an inadequately treated community. (iii) Moreover, "last" cases may obviously also arise by importation from the outside by immigrating persons still infected. Reports have been furnished recently of frank clinical recrudescence of yaws arising from one or more of these sources in some previous mass campaign areas, *e.g.* Haiti (4).

When solely—or almost solely—immunological evidence of yaws is found in surveillance studies after mass campaigns, it becomes important to assess the recrudescence potential of the disease: (i) We have already pointed to the usefulness of immunological age profiles in appraising the community status of yaws, particularly in the child age groups. (ii) Furthermore, there is a proportion of persons with high titre reactive sera, who are more likely to relapse than persons with low antibody titres. In Western Samoa only 0.6 percent of the children and 1.6 percent of the adults had VDRL titres of 16 dils or above and hence had a limited—but still existant—recrudescence potential (8). In contrast to this, 1.6 percent of the children and 5.9 percent of the adults had 16 dils or more (VDRL) in the Midwestern Region of Nigeria (21). There is thus a higher recrudescence potential in Midwestern Nigeria than in Western Samoa. (iii) Finally, a proportion of seroreactive

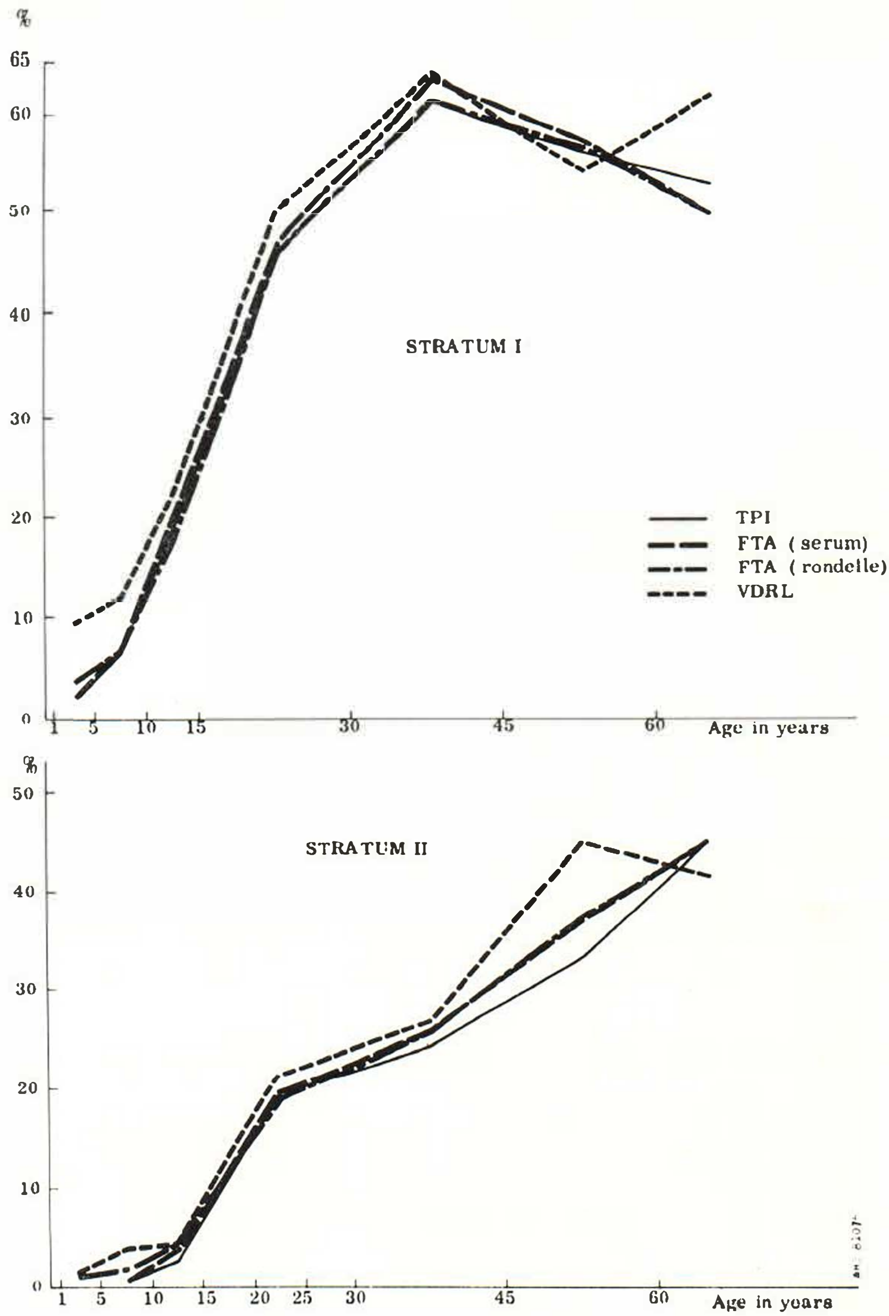

Fig. 16. Sero-reactor rates by stratum and age in TPI, FTA serum, FTA dried blood and VDRL. (a) Reference Laboratory: WHO Endemic Treponematoses Centre, Institut Alfred Fournier, Paris.

children have been found in the surveillance studies to have missed treatment previously. Thus, out of 9.4 percent FTA seroreactors in children in Midwestern Nigeria, four-fifth (that is 7.7 percent, representing 82 percent of the total) had no history of previous treatment. In contrast, in the same age groups in Northern Nigeria, out of 7 percent TPI seroreactive children, only one-third (that is 2.2 percent, representing

31 percent of the total) had remained untreated (1). This corresponds to the collateral information that at the initial treatment survey of the mass campaign, the population coverage was considerably higher in Northern Nigeria than in the Midwestern Region of Nigeria where the recrudescence potential must be considered to be greater. (Environmental changes caused by the current war in Nigeria may well express themselves in new outbreaks of yaws in that country more rapidly than the indices suggest from these investigations undertaken between 1965 and 1967.)

Susceptibles, Yaws and Venereal Syphillis

A number of animals ranging from mice to monkeys have been shown to be susceptible to experimental inoculation with *T. pallidum* in the laboratory, some showing clinical lesions while others acquire latent or so-called "silent" infections. This orientation of research has become important, *inter alia* in Sweden (7) in the study of what appears to be auto-immune phenomena in the treponematoses. To this must be added the recent discovery of a natural reservoir of latent *T. pertenue* in wild, cynocephale monkeys (6). Moreover, it has been shown that the disease may have overt clinical outbreaks in the gorilla in certain parts of Africa (9). The possible significance of these new findings for the epidemiology of yaws in man is as yet not known, but a new orientation has developed for research into the evolution and biology of the treponematoses.

In tropical human populations an increasing number of seronegatives has been generated over the last 10–15 years, following mass campaigns, particularly in children, in spite of the demonstrated continued low-level transmission of disease. On the one hand this growing child population is susceptible to infection—and reinfection—with yaws: on the other hand, it is also susceptible—on reaching puberty—to infection with venereal syphilis, since to a large extent it does not possess the cross-immunity from yaws which characterised previous generations. In hyperendemic areas fifteen to twenty years ago only 10–15 percent of children were susceptible to venereal syphilis on attaining sexual maturity, while today some 90 percent are susceptible. There is preliminary evidence that this new epidemiological situation—in conjunction with other ecological factors recognised increasingly to favour spread of venereal disease—is now setting the scene for an increasing health problem in regard to syphilis in several developing countries.

Outlook

We have so far recognised that in the last 10–15 years extensive benefits have resulted from mass penicillin campaigns in millions of children and adults throughout the tropical world. In these campaigns dermatological indices have been of basic importance. The results obtained are better and longer-lasting than was possible in the arsenicals/bismuth era. But there are reservations to the long-term outlook, even with the use of an "ideal" drug like long-acting penicillin PAM or DBED. The examples given of clinical, immunological and epidemiological findings in representative random surveys in the surveillance of these campaigns indicate that low-level transmission of *T. pertenue* continues in previous yaws areas 10–15 years after their inception. The dictum is confirmed that in developing rural countries it is not possible to treat community disease out of existence on the basis of drugs alone. Broader measures are needed. As the dermatological lesions of yaws are disappearing difficulties arise. The interest of the public wanes and unconcernedness develops in health administrations in integrating continued active control measures into the functions of local health services. But, even more important, the unhygienic environment which maintains transmission of yaws is only slowly—if at all—being improved in a framework which in many developing countries is characterised by economic regression rather than progress—as pointed out by Myrdal (20). It is this broad ecological background—and the environmental influences

—which, in the long run, will determine the cycles of fall and rise of treponemal disease and not only the efficacy of drugs in individual clinical cases—at least until a partially, or entirely, effective immunising vaccine becomes available through intensified research, and for which a rational approach now seems possible.

SUMMARY

Clinical, serological and epidemiological characteristics of *Framboesia tropica* (yaws) are described. Recent trends concerning this and other endemic treponematoses of childhood (pinta and "endemic" non-venereal syphilis) are appraised with reference to mass-campaigns undertaken in 45 developing countries in the frame of the World Health Organization's programme since 1950. In these campaigns—mainly against yaws—some 47 million cases, latents and contacts were treated with long-acting penicillin PAM or DBED.

Community-wide application of long-acting penicillin resulted in rapid regression of disease and changes in clinical patterns. With disappearing dermatological lesions, sero-epidemiological studies are needed increasingly in the surveillance of disease and infection. A description is given of the methodology developed for representative sample surveys and the obtaining of immunological community age profiles in rural tropical populations. An inventory is presented of such studies in several tropical countries. In this context new techniques and equipment were developed for suitable preservation and large-scale shipment of venipuncture serum (deep-frozen in liquid nitrogen at $-200°C$) and of dried capillary blood (rondelle of blotting paper) so as to keep specimens in suitable condition for reagin (VDRL) and treponemal antibody (FTA, TPI) testing in component national and international laboratories. The utilisation of the large tropical serum collections obtained for studies of several conditions (malaria, virus, immunohematology *etc.*) other than yaws ("multipurpose exploitation") is outlined.

The investigations of yaws as a "disappearing disease" in previous areas of different endemicity are illustrated by examples from W. Samoa, Nigeria and other countries. The rapid regression of clinical lesions after penicillin campaigns is followed by slow serological recession. There can be little doubt that the campaigns have given enormous benefits to large numbers of people and that the results are much better and longer-lasting than those possible in the metal therapy era. But the findings show that isolated "last" clinical cases or residual foci of yaws continue to occur. Moreover, FTA and TPI seroreactors rates in children, as well as high-titre VDRL reactivity in a goodly number, indicate that low level transmission continues in most areas and suggest a certain recrudescence potential of the disease. To this human reservoir must be added the recently discovered extra-human reservoir of latent *T. pertenue* in certain wild monkeys, and the possible occurrence of frank disease in gorillas—the epidemiological role of which is as yet unknown.

Following penicillin mass campaigns in rural tropical populations, the age groups attaining puberty are increasingly without the relative cross-immunity from yaws against venereal syphilis present in previous generations. This is a new epidemiological factor to be taken into account—in conjunction with other recent ecological changes recognised to favour spread of venereal disease.

Following disappearance of dermatological lesions in yaws difficulties arise in attitudes towards the disease, particularly the need for post-campaign measures, and the integration of continued surveillance activities into the functions of existing rural health services. However, improvement of hygiene and other environmental conditions is slow and the frame for economic development unsatisfactory—aspects which are restraining rather than facilitating interruption of transmission of *T. pertenue*. Seen against this broader background the cycles of fall and rise of treponemal disease are likely to continue until at least a partially effective immunising agent becomes available through intensified research.

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REFERENCES

1. Antal, G. M.: Report to WHO, 1968.
2. *Bull. Soc. Path. exot. 49:* 1023–81, 1965.
3. Buxton, P. A.: *Researches in Polynesia and Melanesia,* Parts V–VII, London School of Hygiene and Tropical Medicine, p. 85, 1928.
4. Christiansen, S.: Report to WHO, 1967.
5. D'Costa, J. F., Wilkinson, A. E. and Guthe, T.: WHO unpublished document WHO/VDT/RES/68.146, 1968.
6. Fribourg-Blanc *et al.: Bull. soc. Path. exot. 59:* 54–9, 1966.
7. Fredriksson, F., Hederstedt, B. and Rosengren, S.: WHO unpublished working document WHO/VDT/RES/67.117, 1967.
8. Fröhlich, W. and Wang, P. N.: Report to WHO, 1965.
9. Gregory, W. K.: *The Henry Cushier Raven Memorial Volume,* Columbia University Press, 1950.
10. Guthe, T.: *Bull. Wld Hlth Org. 33:* 864–7, 1965.
11. Guthe, T.: *Arch. Immunol. Ther. exp. 14:* 689–703, 1966.
12. Hackett, C. J.: *J. trop. med. Hyg. 60:* 159–68, 1957.
13. Hackett, C. J.: Report to WHO, 1968.
14. Hederstedt, B.: Report to WHO, 1966.
15. Hoff, N. M. van der: *A comparative study of two yaws endemics in South-East Borneo,* Breukelen, Van Dijk (Proefschrift Leiden), 1956.
16. *J. trop. Med. Hyg.* February and March, 1957.
17. Klokke, A. H.: *Yaws in the households of Tiawas (Central Java),* Surabaja, H. van Ingen, 1956.
18. Kranendonk, O.: *Serological and epidemiological aspects in yaws control. Report on a mass treatment campaign against yaws in Netherlands New Guinea,* Amsterdam (Academisch proefschrift), 1958.
19. Lambert, S. M.: *J. trop. Med. Hyg. 39:* 41–6, 1936.
20. Myrdal, G.: *Asian Drama,* Pantheon Publications, New York, 1968.
21. Ruland, N.: Report to WHO, 1968.
22. Vaisman, A.: Report to WHO, 1966.
23. Vaisman, A., Hamelin, A. and Guthe, T.: *Bull. Wld Hlth Org. 29:* 1–6, 1963.
24. Wang, P. N.: WHO unpublished document INT/VDT/66.213, 1966.
25. World Health Organization: *World Health Assembly Resolution WHA 2.36,* 1949.
26. World Health Organization: *Wld Hlth Org. techn. Rep. Ser. 13,* 1950.
27. World Health Organization: *Wld Hlth Org. techn. Rep. Ser. 63,* 1953.
28. World Health Organization: *Bull. Wld Hlth Org. 8:* 1–418, 1953 b.
29. World Health Organization: *Wld Hlth Org. techn. Rep. Ser. 190,* 1960 a.
30. World Health Organization: WHO unpublished document INT/VDT/148, 1960 b.
31. World Health Organization: *Wld Hlth Org. techn. Rep. Ser. 294,* 1965.