Treponemal infections

Report of a WHO Scientific Group

World Health Organization
Technical Report Series
674

World Health Organization, Geneva 1982
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduction</td>
<td>7</td>
</tr>
<tr>
<td>2. Epidemiological aspects</td>
<td>8</td>
</tr>
<tr>
<td>2.1 Syphilis</td>
<td>8</td>
</tr>
<tr>
<td>2.2 Nonvenereal treponematoses</td>
<td>16</td>
</tr>
<tr>
<td>References</td>
<td>19</td>
</tr>
<tr>
<td>3. Clinical aspects</td>
<td>20</td>
</tr>
<tr>
<td>3.1 Venereal syphilis</td>
<td>20</td>
</tr>
<tr>
<td>3.2 Nonvenereal treponematoses</td>
<td>23</td>
</tr>
<tr>
<td>References</td>
<td>24</td>
</tr>
<tr>
<td>4. Laboratory aspects</td>
<td>25</td>
</tr>
<tr>
<td>4.1 Diagnosis</td>
<td>25</td>
</tr>
<tr>
<td>4.2 Microscope tests used to identify treponemes</td>
<td>25</td>
</tr>
<tr>
<td>4.3 Serological tests for the detection of antibodies in individuals with treponemal infections</td>
<td>27</td>
</tr>
<tr>
<td>4.4 Diagnosis of neurosyphilis by cerebrospinal fluid (CSF) examination</td>
<td>34</td>
</tr>
<tr>
<td>References</td>
<td>35</td>
</tr>
<tr>
<td>5. Management aspects</td>
<td>35</td>
</tr>
<tr>
<td>5.1 Treatment of early acquired syphilis</td>
<td>39</td>
</tr>
<tr>
<td>5.2 Treatment of late syphilis</td>
<td>35</td>
</tr>
<tr>
<td>5.3 Diagnosis and management of syphilis in pregnancy</td>
<td>44</td>
</tr>
<tr>
<td>5.4 Treatment of congenital syphilis</td>
<td>45</td>
</tr>
<tr>
<td>5.5 Recommendations for follow-up of patients treated for syphilis, all stages</td>
<td>47</td>
</tr>
<tr>
<td>5.6 Contact treatment</td>
<td>48</td>
</tr>
<tr>
<td>5.7 Penicillin reactions</td>
<td>48</td>
</tr>
<tr>
<td>5.8 Management of nonvenereal treponematoses</td>
<td>50</td>
</tr>
<tr>
<td>References</td>
<td>51</td>
</tr>
<tr>
<td>6. Control aspects</td>
<td>52</td>
</tr>
<tr>
<td>6.1 Objectives</td>
<td>52</td>
</tr>
<tr>
<td>6.2 Syphilis control</td>
<td>52</td>
</tr>
<tr>
<td>6.3 Control of nonvenereal treponematoses</td>
<td>57</td>
</tr>
<tr>
<td>References</td>
<td>59</td>
</tr>
<tr>
<td>7. Research aspects</td>
<td>60</td>
</tr>
<tr>
<td>7.1 Investigation of T. pallidum</td>
<td>60</td>
</tr>
<tr>
<td>7.2 Immunity</td>
<td>62</td>
</tr>
<tr>
<td>7.3 New parameters for the diagnosis of neurosyphilis by cerebrospinal fluid (CSF) examination</td>
<td>63</td>
</tr>
<tr>
<td>7.4 Clinical immune response</td>
<td>64</td>
</tr>
<tr>
<td>7.5 Treatment</td>
<td>64</td>
</tr>
<tr>
<td>7.6 Survival of T. pallidum after therapy</td>
<td>65</td>
</tr>
<tr>
<td>7.7 Genital ulcers</td>
<td>66</td>
</tr>
<tr>
<td>References</td>
<td>66</td>
</tr>
</tbody>
</table>
8. Summary of recommendations ........................................ 67
  8.1 Epidemiological aspects ........................................ 67
  8.2 Clinical aspects ................................................ 68
  8.3 Laboratory aspects ............................................. 68
  8.4 Treatment aspects ............................................. 69
  8.5 Control aspects ................................................ 73
  8.6 Research aspects ............................................... 74
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(Geneva, 6–12 October 1980)

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TREPONEMAL INFECTIONS

Report of a WHO Scientific Group

The WHO Scientific Group on Treponemal Infections met in Geneva from 6 to 12 October 1980. The meeting was opened, on behalf of the Director-General, by Dr I. D. Ladnyi, Assistant Director-General, who stressed the great importance that WHO has always attached to the sexually transmitted diseases and to the nonvenereal endemic treponematoses, because of the heavy burden they impose on society and the individual.

1. INTRODUCTION

In 1975, following the Technical Discussions at the Twenty-eighth World Health Assembly on “Social aspects of sexually transmitted diseases: need for a better approach”, the Health Assembly in resolution WHA 28.58 invited governments to make optimal use of existing services and health structures to strengthen the control of sexually transmitted diseases, including syphilis, and requested the Director-General of WHO to provide Member States with the advice and assistance necessary for a fuller appreciation of the public health aspects of these diseases. In 1978, the World Health Assembly also requested the Director-General of WHO to draw up, disseminate, and update, as required, guidelines on the control of sexually transmitted diseases (resolution WHA 31.57).

Syphilis and the nonvenereal treponematoses were considered in depth by the WHO Expert Committee on Venereal Infections and Treponematoses in 1953 (1) and 1959 (2), and again by the WHO Scientific Group on Treponematoses Research in 1970 (3).

The objective of this latest meeting was to review all aspects of the treponematoses and to provide updated standards and guidelines for their diagnosis, treatment, and control.

REFERENCES

2. EPIDEMIOLOGICAL ASPECTS

2.1 Syphilis

2.1.1 Basic epidemiology

Reported incidences of syphilis depend on disease transmission within given populations and the extent to which interactions between available health services and these populations limit disease transmission. But the extent to which available statistics reflect the incidence of syphilis also depends on case-finding efforts, variations in notification practices, and social factors that may limit, increase, or reduce the interaction between infected individuals and health services (I, 2). Thus, incidence figures, like trends in available data, may or may not accurately reflect the true epidemiology of the disease. Comparisons of trends in syphilis incidence between countries in which the epidemiology of the disease may be quite different are essentially meaningless.

2.1.2 Available statistics

Primary and secondary syphilis are the best defined and most easily diagnosed stages of syphilis. Incidence data for these stages reflect the extent of the problem most closely and make it possible to evaluate measures to control transmission. Unfortunately, only a limited number of countries specify infectious syphilis (i.e., primary and secondary) in their statistical returns. Unless the proportion of infectious syphilis cases to total cases is known, the transmission level of the disease in any population group is difficult to evaluate.

Assuming the reporting errors in each country to be consistent, the data presented in Fig. 1 suggest that few of the countries included were able to reduce the incidence of primary and secondary disease.

Syphilis appears to be a problem of considerably greater magnitude in countries where health services are relatively poorly developed. Unfortunately, statistical data from these countries are scanty.

Some indication of prevalence is provided by the serological testing of selected population groups (Table 1). The majority of cases detected by screening are in either the early or the late latent stage.

The frequency of late complications of syphilis is declining throughout the world.

As regards the future, high prevalence rates for early syphilis can be expected wherever there is social disruption and mass population movements, as in some parts of South-East Asia and Africa. In developed countries struggling with the social consequences of inflation, there has been a levelling off, and in certain cases a fall, in the incidence of gonorrhoea which has sometimes been followed, e.g., in the USA, by a rise in the incidence of infectious syphilis. Elsewhere—for instance, in Singapore, where a growing percentage of local gonococci
Table 1. Reactor rates in serological tests for syphilis

<table>
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<tr>
<th>Country and groupa</th>
<th>No. tested</th>
<th>% reactive</th>
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<tr>
<td>Fiji: antenatal clinics, Suva (1978)b</td>
<td>495</td>
<td>22.0</td>
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<tr>
<td>Brazil: antenatal clinics, Nitrol (3)</td>
<td>200</td>
<td>16.0</td>
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<tr>
<td>Ethiopia (4): antenatal clinics, Addis Ababa (1976)</td>
<td>337</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>general population, rural</td>
<td>250</td>
</tr>
<tr>
<td>Malawi: antenatal clinics and blood donors (5)</td>
<td>22 560</td>
<td>6.1</td>
</tr>
<tr>
<td>Chile: antenatal clinics (6)</td>
<td>21 052</td>
<td>3.4</td>
</tr>
<tr>
<td>Republic of Korea: antenatal clinics (7)</td>
<td>686</td>
<td>3.4</td>
</tr>
<tr>
<td>Malaysia: antenatal clinics, Kuala Lumpur (1973–75) (8)</td>
<td>10 096</td>
<td>2.0</td>
</tr>
<tr>
<td>Nigeria: antenatal clinics, Ibadan (9)</td>
<td>8 024</td>
<td>1.9</td>
</tr>
<tr>
<td>Rwanda: antenatal clinics, Butare (10)</td>
<td>862</td>
<td>1.2</td>
</tr>
<tr>
<td>India: antenatal clinics, Kerala (11)</td>
<td>2 000</td>
<td>1.4</td>
</tr>
<tr>
<td>Sri Lanka: antenatal clinics, Colomboc</td>
<td>17 579</td>
<td>1.1</td>
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<tr>
<td>Australia: antenatal clinics (12)</td>
<td>3 042</td>
<td>0.3</td>
</tr>
<tr>
<td>Poland: antenatal clinics, Bialystok (13)</td>
<td>140 000</td>
<td>0.27</td>
</tr>
<tr>
<td>Federal Republic of Germany (2): newborns</td>
<td>5 000</td>
<td>0.26</td>
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<tr>
<td>United Kingdom: antenatal clinics, Scotland (14)</td>
<td>64 404</td>
<td>0.03</td>
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a "Antenatal clinics" refers to women tested while attending such clinics for examination or delivery.

b Data presented by A. Pennington at a WHO workshop in Suva, Fiji, in April 1979.


are penicillinase-producers, and where drugs other than penicillin are increasingly used—the incidence of early syphilis may be expected to rise.

2.1.3 Homosexual transmission

Homosexual transmission is an epidemiological factor of increasing importance.

In the USA, the increase in infectious syphilis observed between 1969 and 1976 was almost exclusively among men. At the same time,
the proportion of men with infectious syphilis who named other men as sexual partners increased by almost 200% (15). In Australia in 1973, homosexuality accounted for 73.2% of primary and secondary syphilis infections in males (16). In the United Kingdom, the proportion of early syphilis cases which had been acquired as a result of homosexual activity increased from 42.4% in 1971 to 54% in 1977 (17). This association between homosexuality and syphilis transmission appears to be more pronounced in developed countries. Some reports from developing countries—e.g., Sri Lanka¹ and India (18)—also make reference to the importance of homosexual transmission.

The high infection and reinfection rates among homosexuals (14) make this relatively small group an important reservoir of infection which may contribute significantly to the transmission of syphilis in the community at large. Unless the level of infection in this reservoir can be reduced, syphilis control efforts may not have the desired impact in some communities.

2.1.4 Congenital syphilis

In countries that have utilized preventive measures systematically, the congenital form has disappeared or its incidence has stayed low. In certain other countries, which have been unable to institute such measures regularly, congenital syphilis is still a serious disease resulting in fetal wastage, neonatal mortality, and infant morbidity.

China has claimed the total eradication of congenital syphilis, and many countries in both eastern and western Europe (e.g., Poland and the United Kingdom), as well as Japan, have been able to reduce its incidence to very low levels. In countries where the services dealing with sexually transmitted diseases and with maternal and child health are poorly developed, early and late cases of congenital syphilis are encountered in fairly large numbers.

2.1.5 Difficulties in defining the epidemiology of syphilis

(a) Differing concepts

Health personnel have varying concepts of diagnostic criteria, particularly in the case of early and late latent disease. Seroreactivity rates from screening surveys are of uncertain significance, even when

titre levels are specified. The interpretation and the treatment implications of results vary for different groups within large populations.

For example, in the past early latent syphilis was variously defined and a confirmed VDRL titre of 1 in 8 or higher was widely taken as indicating a need for treatment.

(b) Data bias

The proportion of infected individuals who voluntarily attend health facilities is unknown. Nor is it known what proportion of these attenders are identified and reported.

Crude rates mask the divers risks to different groups within a population. Large differences in crude rates may be due solely to the presence of differing groups within a population or to differences in population composition. For example, a population composed only of young men may have a much higher crude rate than one also containing children and women. The rates for young men in both populations may, however, be identical.

2.1.6 Needs

Adequate identification of the size and nature of a local or national syphilis problem requires a statistical system that will provide the following:

1. A standard measurement of disease frequency. The most meaningful is the true annual incidence or morbidity rate (number of cases per 100 000 total population) for early disease.

2. Stratified rates for the major components of a population. Important variables include age, race, sex, sexual preference, social status, and geographical location. When different populations are compared, a summary rate should be adjusted (i.e., standardized) for the composition of each population.

3. Application of all measurements of disease to a reasonably approximate probability sample of the total population. In other words, the amount of disease in the sample should permit a reasonable estimate of the true amount of disease in the population.

4. Improved collection and organization of data.

(a) It is evident that statistics on syphilis need to be more detailed in order to improve their effectiveness in measuring the seriousness of the problem and designing control approaches. In particular, they must separate early infectious syphilis from latent cases, and both of these from late noninfectious syphilis.
(b) If syphilis cases could be reported and summarized by stage, i.e., congenital, primary and secondary, early latent, late latent, and symptomatic late infections, a much clearer picture of trends in prevalence rates could be obtained.

(c) General agreement has to be reached on the definition of "early latent" and "late latent" syphilis.

(d) A standardized form is required to permit widespread collation of statistics.

2.1.7 Recommendations

1. The following categories should be used in reporting cases of syphilis:

   (a) primary and secondary infections,
   (b) early latent infections,
   (c) late latent infections,
   (d) symptomatic late infections,
   (e) congenital infections in patients under 2 years of age,
   (f) congenital infections in patients 2 years of age or older.

Early latent syphilis means asymptomatic seroreactive syphilis of not more than 2 years' duration. All other latent cases are defined as late latent. Sequential serological examinations after treatment may be helpful in separating early and late latent syphilis, e.g., a fall in VDRL titre to negative within 1 year of adequate treatment would suggest early latent syphilis. A history of primary or secondary lesions would allow more accurate timing of the duration of the disease.

The prerequisites of a diagnosis of latent syphilis are: no clinical evidence of active syphilis of any system, normal cerebrospinal fluid, and a chest X-ray showing a cardiovascular shadow free from evidence of syphilis. (It is appreciated that facilities permitting all these criteria to be fulfilled are not always available.)

2. This classification should be considered by WHO and relevant nongovernmental organizations including the International Union against Venereal Diseases and Treponematoses (IUVDT) and taken into account when the International Classification of Diseases is reviewed.

3. Incidence rates for early syphilis (the sum of primary, secondary and early latent cases) should be collated:

   (a) by age group in years (under 10, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–49, 50 and over),
   (b) by sex (M/F),
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| Brazil                      |      |      |      |      |      |      |      |      |      |
| Colombia                    | 18   | 67   | 73   | 22   | 55   | 131  | 144  | 127  | 642  |
| Dominica                    | 351  | 206  | 72   | 32   | 7    | 3    | 28   | 7    | 2    |
| Dominican Rep.              |      |      |      |      |      |      |      |      |      |
| Ecuador                     | 437  | 380  | 337  | 505  | 364  |      |      |      |      |
| Grenada                     |      |      |      |      |      |      |      |      |      |
| Guatemala                   |      |      |      |      |      |      |      |      |      |
| Guyana                      |      |      |      |      |      |      |      |      |      |</p>
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<sup>1</sup> No information available.  
<sup>2</sup> No cases reported.  
<sup>4</sup> 11 months only.  
<sup>5</sup> 10 months only.  
<sup>6</sup> Provisional data.  
<sup>8</sup> 8 months only.  
<sup>e</sup> Latent years.  
<sup>f</sup> Metheu, A. Z. Unpublished information.  
(c) by other epidemiological parameters helping to distinguish the incidence in different groups.

2.2 Nonvenereal treponematoses

2.2.1 Basic epidemiology

The prevalence of nonvenereal treponematoses—yaws, pinta, and endemic syphilis—has undergone dramatic changes over the past three decades (20, 21, 22, 23, 24; Centers for Disease Control, unpublished information). The first change was a precipitous decline in the prevalence of active and latent infections brought about by the mass treatment campaigns of the 1950s and 1960s. An estimated 152 million people were examined in those campaigns, and 46.1 million clinical and latent cases, as well as contacts, were treated with long-acting penicillin preparations (20). The campaigns halted transmission of infection in many areas, and held out a promise of ultimate yaws eradication if intensive surveillance for active infectious cases was continued during the final (consolidation) phase of the campaigns.

Over-impressed by the rapid decline in cases of nonvenereal treponematoses following mass treatment and subsequent resurveys, some countries prematurely delegated surveillance activities to the static rural health services, often without adequately training the staff for their new task. The resulting discontinuation of adequate surveillance has brought about the re-establishment of endemic foci in a number of countries, particularly in West Africa (Centers for Disease Control, unpublished information) and Central Africa, but also in South-East Asia (Table 2). A deteriorating economy has usually accompanied this development, leading in turn to the curtailment of active case-finding. In some areas, limited health care resources were diverted to the control of other diseases (e.g., cholera, malaria, schistosomiasis) with higher morbidity or mortality rates than the nonvenereal treponematoses. Finally, the growth and increasing mobility of populations have placed severe limitations on the control methodology so successfully employed in the past.

The clinical cases of nonvenereal treponematoses that are identified and reported by the health service may reflect the epidemiological situation to only a limited extent. Detection depends on the accessibility of the primary health care service, the availability of treatment, and the intensity of case-finding activities in the community. It has
also been observed that, in foci of infection where up to 80% of the population showed serological evidence of infection, only a few clinical cases could be identified. This phenomenon of “attenuated” treponemal infection, in which the duration and numbers of clinical lesions are reduced, is not fully understood. Only a sero-epidemiological survey of a large population sample would provide the information on endemicity necessary for designing an effective control programme.

2.2.2 Available statistics

Recent country reports concerning yaws reveal marked variations in prevalence since the mass treatment campaigns (Table 2). Patchiness in distribution and persistent foci beyond the reach of static health services continue to be epidemiological characteristics of the disease.

The incidence of the other treponematoses differs according to disease and the geographical region, but they show epidemiological characteristics similar to those of yaws.

Pinta continues to decrease in prevalence and is at present restricted to a few areas in southern Mexico, Central America, and Colombia (21, 22, 23, 29), although there has been only limited surveillance in the past decade (Table 3).

| Table 3. Cases of pinta reported in Colombia and Mexico, 1971–78 |
|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Colombia          | 257 | 200 | 191 | 149 | ... | ... | ... | ... |
| Mexico            | 503 | 377 | 357 | 248 | 112 | 99  | 81  | 32 |

Endemic syphilis has also decreased in prevalence throughout the world (30), but a few foci of infection still exist in Africa, Australia, and western Asia. In a recent WHO survey, the number of early cases of endemic syphilis in Mali, Mauritania, Niger, and Upper Volta was estimated at many thousands, suggesting that endemic syphilis may be a much greater problem in the sub-Saharan area than it used to be.

2.2.3 Africa

In Africa, especially West Africa, some foci of nonvenereal treponematoses have persisted, and in others intensified transmission
and a spread of infection to neighbouring areas have occurred in what appears to be a great resurgence of yaws. Benin reported 10,455 cases of yaws in 1979; Ghana, over 70,000 cases in 1976; Ivory Coast, 10,671 cases in 1978; and Togo, 2,670 cases in 1979 (Centers for Disease Control, unpublished information). Mali reported 31,476 cases of endemic syphilis in 1976, and Niger reported 1,855 cases of endemic syphilis in 1977 (information from Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies, and from Centers for Disease Control, USA). In a recent WHO survey in the Central African Republic, Congo, and Gabon, clinical yaws was detected in over 20% of the Pigmy population, and positive serological tests were obtained in 80%.

Contrary to expectations, the socioeconomic status of a large segment of the population in the rural areas of West Africa has either not improved or has actually regressed in the past decade. In these areas, patients with reported yaws infection now number tens of thousands, but epidemiological estimates place the true incidence of the disease as four times greater.

In the areas of increasing prevalence, atypical early yaws lesions may be underdiagnosed owing to the inexperience of clinicians unfamiliar with the manifestations of the disease.

2.2.4 The Americas

In the Americas, reported yaws incidence is very low with small foci remaining on the mainland in Brazil, Colombia, Ecuador, Guyana, and Suriname (25), and in a few islands including Dominica and Haiti (29). Cases of yaws were recently reported in Martinique (27). Brazil reported 118 cases of yaws in 1974 (26). Pinta still exists in Colombia (22), and in southern Mexico.

2.2.5 Asia and the Pacific

The antiyaws campaign in its different phases still continues in Indonesia (A.Z. Meheus, unpublished information), where it has succeeded in completely interrupting transmission on some of the larger islands. During survey and surveillance activities, only 2,781 cases of yaws were identified in 1976 compared with 37,644 in 1971 (Table 2). Similar trends are reported from Papua New Guinea and the South Pacific (28). There are some reports of persistent, low-level yaws in Democratic Kampuchea, Bougainville (Papua New Guinea),
and Sri Lanka. In western Asia, a recent serological survey in Saudi Arabia identified a focus of what is believed to be intensive transmission of endemic syphilis (31).

2.2.6 Needs

Typically, nonvenereal treponematoses are confined to underserved and underprivileged population groups in the tropical belt. Lack of interest and lack of data on the extent of the problem and its growth have prevented the implementation of appropriate control measures. Past experience suggests that the earlier the growing need is met, the more cost-effective such measures are likely to be. This aspect should be given due consideration.

2.2.7 Recommendations

1. Health administrations in tropical countries should keep themselves constantly informed on the extent of nonvenereal treponematoses, and put relevant data, including information on foci of infection, at the disposal of neighbouring countries so that they, in turn, can take measures to prevent the reintroduction and spread of these diseases.

2. WHO should act as a clearing-house for surveillance data received from Member States in accordance with World Health Assembly resolution WHA31.58.

3. Affected countries should reconsider the priority given to the control of nonvenereal treponemal infections.

REFERENCES


19
3. CLINICAL ASPECTS

3.1 Venereal syphilis

3.1.1 Early syphilis

The Scientific Group agreed that the manifestations of untreated early syphilis had not changed since they were described in the classic monograph of Stokes et al. (1) published in the years immediately preceding the era of antibiotics and steroid drugs. Since the introduction of these medicaments, atypical or modified early lesions are occasionally observed. Sometimes antibiotic treatment, adequate for another infection in a patient who coincidentally is incubating syphilis, extends the incubation period and alters or masks the appearance of early syphilis.

If there is any difference between the disease of today and that of former years, it expresses itself in the form of patient discomfort.
Classically, the lymphadenopathy that accompanies the chancre is painless, but today patients more frequently complain of pain associated with the swellings and the ulcers. This fact could reflect concomitant infection with other sexually transmitted agents, e.g., the herpes virus. The old adage that secondary skin rashes are symptom-free remains true with few exceptions, although some patients may have an associated pruritus.

Another change in early syphilis, unrelated to treatment, concerns the site of the primary lesion. While genital lesions continue to dominate the clinical scene, in recent years, with changing sexual practices, the frequency of extragenital chancre has increased, with anal lesions predominating.

Syphilis is seldom contagious for more than four years. Secondary skin and mucous membrane manifestations of varying infectivity may alternate with periods of latency (see section 2.1.7 for definitions).

3.1.2 Late syphilis

As a result of incidental antimicrobial therapy, syphilis control efforts, and the widespread use of appropriate therapy, late syphilis has become a relatively infrequent disease. Certainly, the severely disabling neurosyphilitic conditions are now seldom seen. For example, only 55 patients with neurosyphilis were identified in Denmark in the past decade (2).

The cases of late syphilis currently being identified are for the most part being recognized early in their symptomatic stage. As in earlier times, they present a wide spectrum of clinical pictures, amply supporting Sir William Osler’s description of syphilis as the great imitator. All too frequently, however, the index of suspicion for syphilis in physicians is low and the patient is labelled with a sophisticated but incorrect diagnosis. Recognition of the disease therefore remains a major problem. This is particularly so in patients with psychiatric or neurological illness, and also in cardiac patients with aortitis. Patients with these conditions seldom give a history of antibiotic treatment, suggesting that such treatment for whatever purpose is effective in preventing the development of late symptomatic syphilis.

3.1.3 Congenital syphilis

Despite the fact that congenital syphilis can be completely prevented by the detection and treatment of infected women during
pregnancy, it still occurs with distressing frequency in many parts of the world. A woman with early active syphilitic infection will almost invariably infect her unborn infant by haematogenous spread of treponemes to and through the placenta. Whether or not syphilis in the fetus follows first-trimester infection with \textit{T. pallidum} is still debated (3, 4). If it does, spontaneous abortion is most probably the outcome. This is the most likely course when infection is acquired in the second trimester from an expectant mother with early syphilis. Intrauterine infection is the one type of syphilis with a high mortality rate; only infants who acquire their infection late in gestation, or who manage to suppress it (in some, as yet unknown, fashion), reach gestational maturity. In the majority of these infants, syphilitic infection is clinically inapparent at birth, but makes itself evident in the first few weeks or months of life. The clinical manifestations of early congenital syphilis are in no way different from those of former years. Failure to diagnose an infected infant is more often due to unfamiliarity with the disease rather than to an atypical or altered clinical picture.

3.1.4 \textit{Genital ulceration in tropical areas}

Particularly in tropical areas, genital ulcers are a frequent cause of patient consultation and may be due to one or more infections, including syphilis, chancroid, herpes genitalis, granuloma inguinale, lymphogranuloma venereum, amoebiasis, and a variety of bacterial and fungal infections. All these call for different diagnostic and treatment approaches. In the absence of adequate laboratory facilities, diagnosis is often made on clinical grounds.

The prevalence of the various etiological agents differs from country to country. The Group was informed of WHO-supported research being carried out in one tropical area (a) to identify frequencies of the different etiologies of genital sores in a limited number of patients, (b) to identify the associated clinical pictures, and (c) to evaluate effective treatments. The aim is to provide information and develop practical criteria for patient management when laboratory facilities are lacking (see section 7.7).

3.1.5 \textit{Needs}

While antimicrobial drugs have had a major effect upon the incidence of syphilis, they have also reduced the diagnostic and clinical experience of this disease on the part of the physician and lowered his
level of awareness and concern. The major need is to improve case
detection. As in the past strong reliance upon laboratory procedures
continues, and there is still room for more specific and reliable sero-
logical tests. However, it is in the area of clinical suspicion of syphilis
that the greatest need for improvement lies.

The smaller number of cases of early syphilis now encountered in
many countries poses the dilemma of how to educate the physician in
the absence of clinical material. This, with the lack of interest in
teaching venereology in medical schools, has resulted in a whole
generation of physicians whose knowledge of syphilis is woefully defi-
cient.

3.1.6 Recommendations

1. Improved methods for teaching (including audiovisual aids)
should have the highest priority, emphasis being placed on basic facts.
For example, medical curricula should emphasize the use of darkfield
microscopy in all cases of genital sore and teach students to suspect
the disease especially if non-pruritic rashes appear on the palms and/
or body.

2. Case detection should be intensified, with particular attention to
prevention of congenital infection.

3. As neurosyphilis is rarely associated with a history of early
syphilis or well-known clinical signs or symptoms, serological exami-
nation should be routinely performed on patients with neurological
and psychiatric diseases. If the serological test is reactive, a cerebro-
spinal fluid examination should be made to confirm the diagnosis.

4. Syphilitic aortitis should be considered in all cases of abnormal
X-ray findings of the aorta. Patients should be investigated serologi-
cally. A cerebrospinal fluid examination is also advised because con-
comitant neurosyphilis often occurs.

3.2 Nonvenereal treponematoses

3.2.1 Clinical changes

It has been reported that, in areas where yaws has reappeared or
is of low endemicity, relatively mild forms of early lesions can be ob-
served, contrasting with the more florid multiple lesions of former
years (5). Whether or not the devastating late lesions will follow this
relatively mild form of early disease (if it is left untreated) is un-
known. It can be assumed that, with the changing appearance of early yaws infection and the waning familiarity of medical personnel with the disease, a considerable number of clinical cases may not be recognized (5).

So far as the Scientific Group is aware, no changes in the clinical expression of endemic syphilis and pinta have occurred in recent years, apart from an even greater preponderance of latent cases in areas of receding endemicity.

3.2.2 Needs

Medical personnel working in (former) treponematoses-endemic areas need to be trained to identify clinical cases of nonvenereal treponematoses. They also must be made aware of the atypical and milder clinical expressions of yaws lesions that are now more frequent. An atlas of yaws lesions published by WHO twenty years ago (6) has proved extremely useful but is no longer available, except in libraries.

3.2.3 Recommendation

With the recrudescence of yaws in some areas and the continued maintenance of endemic foci of other nonvenereal treponematoses, there is an urgent need for an atlas of yaws, pinta, and endemic syphilis lesions. Illustrations of the common lesions now encountered should be in colour. Conditions important to differential diagnosis should also be illustrated.

REFERENCES

4. LABORATORY ASPECTS

4.1 Diagnosis

The diagnosis of a primary or secondary treponemal infection should be established by identification of the causative organisms using darkfield microscopy. A reliable nontreponemal serological test has confirmatory value in such circumstances. A combination of nontreponemal and treponemal serological tests is essential for the diagnosis of all other stages of syphilis. In countries with limited health care and laboratory services, the diagnosis of treponemal disease is difficult. To achieve some measure of control, particularly of the infection and its further transmission, basic laboratory services, e.g., darkfield microscopy and serological testing by nontreponemal tests, are essential.

However, for many who deal with genital ulcers and suspicious rashes in outlying rural areas, laboratory services may not be available and logistical problems may be such that even the transportation of specimens to laboratories is impracticable. In clinical outposts where nonmedical health workers deliver health care, simple clinical algorithms may help to ensure that genital ulcers and other clinical manifestations of treponemal infections are treated at once with adequate doses of suitable penicillin preparations. Sexual contacts of the patients should receive identical therapy.

4.2 Microscope tests used to identify treponemes

4.2.1 Darkfield

The infectious stages of treponemal infections can usually be diagnosed most quickly and effectively by microscopical demonstration of motile treponemes in wet preparations of serous exudate expressed from suspected primary or secondary lesions. Where topical antibiotics have been used, examination of material obtained by lymph gland puncture may prove useful.

Any ordinary brightfield microscope can be converted to one with darkfield illumination by replacing the brightfield condenser with a suitable darkfield condenser and centring the field of illumination. Any microscope used for darkfield microscopy should be equipped with an adequate source of illumination because of the very low efficiency of light transmission through a darkfield condenser. The
domestic electricity supply is the usual source. Low-voltage (10–12 V), low-wattage lamps of either an incandescent type or the halogen type (as used in motor vehicles) adaptable to DC current or to batteries, as used in vehicles, can meet requirements. Reflected sunlight can be used in outlying tropical areas. Failure to achieve adequate illumination in the field is the sole difficulty associated with darkfield microscopy. It is not, however, a procedure to be put in the hands of untrained personnel. It is necessary not only to know the principles of darkfield illumination and basic microscopy, but also to be familiar with the morphology of various treponemes and know how adequate samples can be safely prepared (1, 2).

Readily portable field microscopes are available but most are expensive.

4.2.2 Identification of Treponema pallidum

Silver staining of specimens formerly provided a means of identifying treponemes in dried preparations and/or tissue specimens. This method has been superseded.

Immunostaining by direct fluorescent antibody staining provides a more definite approach to diagnosis, but it is more time-consuming and requires trained personnel and sophisticated laboratory facilities. Air-dried smears obtained from lesions may be submitted for immunostaining.

4.2.3 Needs

The greatest need is to improve the capability of health care units to identify treponemes.

4.2.4 Recommendations

1. The preferred diagnostic test for infectious treponemal disease should be darkfield microscopy.

2. The provision of darkfield condensers and light sources for existing microscopes to an extended number of clinical facilities serving high risk populations should be encouraged.

3. Training in the use of darkfield microscopy and associated skills should be part of the basic training of the relevant health workers.

4. Where conventional microscopes are not suitable, field microscopes should be considered.
4.3 Serological tests for the detection of antibodies in individuals with treponemal infections

4.3.1 *Humoral immune response to different types of treponemes*

Any consideration of serological tests in treponemal infections should commence with the categorical statement that no laboratory means is yet available for distinguishing one treponematosis from another. There is no demonstrable immunological difference between the three currently recognized species of human pathogenic treponemes, and indeed the immune responses to all of them appear to be the same. For this reason no distinction need be made between the diseases, when considering serological tests for their detection.

The various methods used to measure antibody responses in treponemal infection can be divided into two major categories: (a) those that measure antibodies against lipoidal antigens, and (b) those that measure antibodies stimulated by one or more of the antigenic components of the treponeme responsible for the disease. The latter antibodies may be further divided into those generated by specific antigens present only in pathogenic treponemes and those shared with nonpathogenic treponemes (group antibodies). This distinction has significance in so far as different types of antibodies may influence the results of several serological tests (3).

4.3.2 *Tests to detect antibodies to lipoidal antigens*

Of the numerous tests that detect antibodies to lipoidal antigens only a few are in relatively wide use at the present time. Of these, the complement fixation tests (e.g., the Wassermann test) are now the least used as they appear to offer no advantage over the modern flocculation tests (e.g., the VDRL and RPR tests), which are much simpler, quicker, and cheaper to perform. To achieve greater uniformity in test results, the complement fixation tests should be discontinued.

It was the consensus of the Group that the VDRL test should be given preference, as the vast majority of laboratories use the defined antigenic mixture of cardiolipin, phosphatidyl choline, and cholesterol and employ the recommended technique.

Less technically demanding (no microscope necessary) is the rapid plasma reagin (RPR) card test, or one of its variations. This test uses a carbon-containing cardiolipin antigen. The RPR can be performed in laboratories and clinics when facilities are limited. A method based
on a fingerprick sample is available. Microtubes and filter-papers have been used for sending blood samples to laboratories. A more recent method uses glass-fibre discs. These are easily transported and should be considered for use by primary health workers in outlying rural areas.

An initial reactive result with any nontreponemal test on undiluted serum provides a qualitative measure of the presence of antibody. It is important to note that the degree of clumping is not a measurement of reactivity. A reactive or weakly reactive qualitative reaction should be followed by a quantitative determination of antibody.

The lipoidal antigen tests, though admittedly of limited specificity for treponemal infection, remain valuable for the diagnosis of the treponematoses because of their conversion to reactivity and their predictive value for disease activity. Their simplicity and economy are additional virtues. They should continue as screening or first-line procedures for both routine diagnosis and mass screening programmes.

4.3.3 Tests using T. pallidum antigens

Because of the limitations of the lipoidal antigen tests, more specific tests for the detection of antitreponemal antibodies must also be conducted before a definitive diagnosis of treponemal disease can be established.

Currently there are only two treponemal antibody tests in general use for diagnostic purposes. These are the Treponema pallidum haemagglutination (TPHA) and fluorescent treponemal antibody absorption (FTA-ABS) tests, each with several variations. It is generally agreed that the TPHA test is the simpler and less expensive of the two. It rarely becomes positive as early in the course of primary syphilis as the FTA-ABS test, owing to the variable IgM-binding capacity of the TPHA reagents. Furthermore, in primary syphilis, it is theoretically possible that small amounts of IgM antibody produced in response to pathogenic treponemes add to the small amounts of already circulating antibody due to the presence of indigenous non-pathogenic treponemes so that the FTA-ABS test becomes reactive sooner.

Although the Treponema pallidum immobilization (TPI) test was the first treponemal antibody test, it is now regarded by many as no longer routinely applicable in the diagnosis of treponemal diseases. It is time-consuming, expensive, and technically demanding. The information it provides can now be obtained by the other less complex and
less expensive tests already mentioned. There are, however, a few laboratories where the TPI test is still considered of value in some situations, and they continue to perform it on selected sera for research purposes.

4.3.4 Screening

With the widespread application of serological screening, latent syphilis is the most commonly diagnosed stage of the disease in many countries. The continuous serological screening of pregnant women, blood donors, and recognized “at risk” groups serves as a vital tool for establishing syphilis control. Thereafter, the procedure is capable of monitoring and maintaining control at modest cost. The Group felt that, in the present and anticipated epidemiological situation (see section 2), serological screening should be maintained. It should be strengthened wherever it has potential for improving the levels of prevention of congenital syphilis and the costly late stages of the acquired disease.

Screening detects late as well as latent disease. Two recent studies in 72 patients with neurosyphilis noted that 82% of them were detected by routine serological testing. A total of 13 (18%) only were aware of having had early infection (4).¹

The VDRL and the RPR tests are the most widely used screening tests.

The TPHA test, because of its ease of performance and its high sensitivity and specificity, is rapidly becoming the preferred treponemal antibody test. Its low cost compared with the FTA-ABS test, and its ability to detect individuals with treponemal infections who are nonreactive to lipoidal antigen tests, make it useful as a screening test. However, because it may be slow to become reactive in early syphilis, it should not replace the lipoidal antigen tests.

In some parts of the world the VDRL and TPHA tests are both used in initial screening procedures; in other areas, with a low prevalence of syphilis and many previously treated patients, the two tests are used sequentially.

The Group felt that there was good reason to urge that initial screening procedures include both a lipoidal antigen test and the TPHA. While this would entail additional cost, it would provide the

best coverage of all categories of treponemal infection, and when both tests were reactive (or nonreactive) no further testing would be required in most patients.

4.3.5 Confirmation of diagnosis

When the VDRL and TPHA results do not agree, the FTA-ABS test can provide additional diagnostic help. Restricting the use of the FTA-ABS test in this way would reduce the frequency with which this more complex test is performed. Indications for the use of the various serological tests are summarized in Table 4.

Table 4. Indications for different types of serological test

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<thead>
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<tr>
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<td>Lipoidal antigens</td>
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<td>Diagnosis</td>
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<td>Activity of infection</td>
<td>VDRL or RPR</td>
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<td>Response to treatment</td>
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4.3.6 Response to treatment

The lipoidal antigen tests primarily reflect disease activity, and serial quantitative performance of these tests provides the best means of measuring response to treatment in most stages of treponemal infection.

When a diagnosis of treponemal infection has been made and effective treatment given, there is little to be gained from further treponemal antibody testing because the reactions remain positive with little change for long periods of time. The finding of a reactive treponemal test alone (TPHA and/or FTA-ABS) is not necessarily an indicator of active disease or need for treatment (see section 4.3.8).

4.3.7 Recommendations

1. For screening and diagnostic purposes, two tests, one using a lipoidal antigen and the other a treponemal antigen, are the best choice, e.g., the VDRL or RPR test (or an automated equivalent) and the TPHA test (or an automated equivalent).
2. In conditions of high prevalence and limited resources, either the VDRL or RPR test should be used for screening.
3. The lipoidal test should be quantitated when positive.
4. The TPHA test should be used to detect late treponemal disease, for which it is particularly sensitive.
5. The FTA-ABS test should be reserved for sera giving discrepant results in initial testing.
6. The TPI test is no longer necessary as a confirmatory test for the treponematoses. It might be useful to maintain it in a few laboratories for research purposes.

4.3.8 Detection of T. pallidum-specific IgM

In the belief that detection of specific IgM denotes active syphilis, research has been carried out to find a reliable means of determining which test results indicate active infection, and thus a need for treatment, and which indicate adequately treated or “burnt-out”, inactive disease.

(a) The FTA-IgM test

The FTA-IgM test may be helpful in the detection of IgM antibodies which develop in the course of syphilis. This test, however, may occasionally give nonspecific reactive results, owing to the presence in serum of anti-IgG globulins (rheumatoid factor). False negative reactions may occur as a result of competitive inhibition of IgM by IgG (5, 6, 7, 8). Thus the use of the test in the diagnosis of syphilis, particularly in the elderly and in cases of early congenital syphilis, has given rise to problems.

Gel-filtration has been used to separate the immunoglobulin fractions in serum before testing. Evidence accumulated in two laboratories (9) during the past 3–4 years strongly suggests that nonspecific reactivity and false negative results do not occur when the isolated 19S (IgM) fraction is used in the FTA-IgM test. This method of detecting the treponemal specific fraction is called the 19S IgM FTA test.

However, it is a time-consuming method, requiring highly qualified personnel and expensive equipment. It can therefore only be performed in research laboratories and on a limited number of samples.

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(b) The 19S IgM SPHA test

A solid phase haemadsorption (SPHA) assay, using μ-chain-specific antisera and the TPHA reagents, has been developed (10) and is currently under study.

In this test, sheep erythrocytes coated with fragments of T. pallidum are used as indicators for the detection of 19S IgM antibodies fixed to solid phase of a μ-chain-specific antiserum on polystyrol plates. This test is easy to perform. Some doubts, however, remain as to its sensitivity.

4.3.9 Needs, standardization of reagents

There is an urgent need for better and more widespread proficiency testing of all laboratories performing serological tests for treponemal infection. Whereas reproducibility may be very high within any given laboratory, the results from comparative testing in different laboratories have shown a distressing lack of conformity and reproducibility. This absence of uniformity may be related to variations in reagents, test performance, and/or control sera. As a first step in improving proficiency testing, there is a need for a series of standard test reagents.

Efforts to standardize pools of control sera have, not surprisingly, proved difficult. In the 1950s, the WHO Serological Reference Centre in Copenhagen cooperated with the WHO Expert Committee on Biological Standardization, and, after international collaborative studies, the International Standard for Human Syphilitic Serum (ISHSS) was established in 1958. It gave serologists the opportunity to express reactivity in International Units (I1). The present-day value of the ISHSS has been questioned.

While a great deal of progress has been made towards global uniformity, much still needs to be done. Two main reference centres have emerged. The Centers for Disease Control in Atlanta, GA, USA, have done notable work in the field of international evaluation studies and training. The WHO Collaborating Centre for Research on Endemic Treponematoses in Paris has provided many countries with samples of serum from a pool tested by eight laboratories.1 These centres

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have not made it clear, however, how their standards compare with the ISHSS or whether they regard their control samples as comparable.

If the aim is international uniformity, then the need is for a single agreed standard.

4.3.10 Recommendations

1. The RPR and other reagin tests should be standardized in terms of the VDRL titre.

2. "Automated" methods should be evaluated with a view to achieving results comparable to those obtained with the standard manual method.

3. Antigen used in the TPHA procedure should be standardized, using reference sera, and the different antigens used should be indicated by additional code numbers or letters.

4. Governments should be encouraged to establish national reference laboratories with responsibility for monitoring laboratory performance.

5. Exchanges of individual sera between laboratories for comparative testing should be encouraged. Split specimens can be used for this purpose.

6. There is a need to harmonize the performances of the main internationally recognized laboratories. There is also a need to compare and harmonize their results, and perhaps to establish a new ISHSS. It may be necessary to produce a separate control serum for each individual serological test, e.g., the VDRL, TPHA, and FTA-ABS tests.

7. Test results standardized against an ISHSS should be reported in International Units (IU), defined as the reciprocal of the highest final dilution producing a 4+ reactivity. Thus a serum with VDRL reactivity equal to that of the ISHSS would be reported as "16 VDRL IU".

8. Laboratories whose results do not conform with those for an ISHSS should review their reagents and methods and take appropriate action.

9. All reagents should be subjected to pre-market assay by an independent authority.
4.4 Diagnosis of neurosyphilis by cerebrospinal fluid (CSF) examination

4.4.1 Limitations of existing tests

The traditional methods of diagnosing neurosyphilis by cerebrospinal fluid (CSF) examination used to be: VDRL test, cell count, and determination of total protein and globulin, as well as the goldsol and mastix curves. The last two methods have now been discarded because the results are not always precise or reproducible. The VDRL test is not a reliable indicator because it is nonreactive in 30–57% of samples from patients with active neurosyphilis (12, 13). Cell counts exceeding 5 cells per mm³ and total protein values above 40 mg/ml are signs of inflammation, but are nonspecific as indicators of syphilitic involvement of the central nervous system (CNS).

Reactivity to tests using treponemal antigens, particularly to the FTA-ABS test and/or the TPHA test, may be caused by a transudation of *T. pallidum*-specific IgG from the serum in patients with adequately treated disease and is therefore not necessarily a sign of active CNS involvement. On the other hand, nonreactivity of the CSF to these assays in all probability excludes the diagnosis of neurosyphilis.

The lack of an indicator for accurate recognition of CNS involvement in treponemal infection has led workers to conduct further investigations in the search for a specific parameter of activity (14, 15). The 19S IgM SPHA reaction may prove useful in the diagnosis of neurosyphilis based on the premise that treponeme-related IgM antibody in cerebrospinal fluid is an accurate indicator of active treponemal CNS disease. Even more intriguing is the suggestion that repeated quantitative assays such as the TPHA index (i.e., the CSF-TPHA titre in relation to the blood/CSF barrier function) over a period of time may prove an excellent measure of response to treatment. This procedure deserves further evaluation and is described more fully in section 7.

4.4.2 Recommendations

1. The cell count and determination of total protein should be used as indicators of inflammation in the CNS and as indicators of response to treatment.

2. Research should be further pursued with the aim of determining more accurately the presence or absence of active neurosyphilis.
REFERENCES


* For detailed reviews of syphilis serology, see: HARRIS, J. R. W., ed. Recent advances in sexually transmitted diseases. Edinburgh, Churchill Livingstone, 1981. Basic research is dealt with in the chapter by A. E. Wilkinson (pp. 79–91), and recent developments in routine diagnostic procedures in the chapter by A. Notowitz & H. E. Menke (pp. 93–100).

5. MANAGEMENT ASPECTS

5.1 Treatment of early acquired syphilis

5.1.1 Treatment with penicillin

(a) Basic data

Penicillin acts on the cell wall of dividing organisms. It lacks toxicity and gives rise to few serious side-reactions. After nearly 40 years, it remains the drug of choice in the treatment of all forms of syphilis.
Although the basic studies of the time/dose relationship of penicillin and *T. pallidum*, undertaken between 1948 and 1950 (1, 2, 3, 4), have not recently been reconfirmed, it is still generally accepted that: (a) in the early infection, a minimum level of 0.03 unit of penicillin/ml\(^1\) of serum must be maintained continuously for at least 7–10 days; (b) should it fall below that level for more than 24–30 hours there is a risk that the treponemes will multiply.

(b) *Pharmacological considerations*

It is important to ensure penicillin serum levels satisfying the basic requirements in all circumstances, without high and pointless peak levels. As *T. pallidum* is sensitive *in vitro* to quantities of penicillin equal to or lower than 0.01 unit/ml, the chosen minimum level of 0.03 unit/ml provides a good margin of safety and can be maintained by injections of various types of long-acting penicillin.

Preparations of penicillin given orally are not preferable to injectable preparations, because of poor patient compliance and lower serum levels due to less certain absorption from the gastrointestinal tract.

Although only serum levels of penicillin are referred to here, the aim of treatment is to destroy treponemes not only in the blood but also in the tissues, particularly the lymphatic and nervous systems. Little information is available concerning concentrations of penicillin in human tissues, even though this aspect has assumed greater importance since persistent forms of treponemes were discovered (5).

(c) *Sensitivity of T. pallidum to antibiotics*

Clinical experience backed by laboratory investigations suggests that *T. pallidum* has remained fully susceptible to penicillin: the vast majority of so-called failures of penicillin treatment are actually reinfections. It is an open question whether *T. pallidum* has the genetic capacity ever to develop resistance to antibiotics; its sensitivity to antibiotics cannot be precisely measured or monitored since the pathogenic organism cannot be cultured *in vitro*.

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\(^1\) The former International Standard for Penicillin was officially discontinued in 1968. However, the former International Unit (0.0006 mg) has continued to be extensively used in the literature and is the unit for penicillin used throughout this report.
(d) Choice of penicillin preparation

Although all of the many penicillin preparations have a comparable action, the basic aim is to maintain a minimum penicillin concentration of 0.03 unit/ml in serum for 7–10 days in early infections (a period that may be extended to 15–20 days in late syphilis cases if a wide safety margin is sought). The chosen preparation should also have a low incidence of side-effects, be readily available and of relatively low cost, and store well under varied climatic conditions. This has led to the choice of preparations which have slower absorption rates. Aqueous procaine penicillin G provides adequate serum levels when daily injections of 600 000 units are given. Procaine penicillin G in oil with aluminum monostearate (PAM) and benzathine penicillin G both permit single-session treatments with considerable epidemiological advantage. The use of PAM has declined, and in some areas it is no longer commercially obtainable. Moreover, there is little to indicate whether some of the preparations available meet WHO specifications.

Benzathine penicillin G gives a reliable prolonged serum level with a single dosage. This preparation has been widely used, particularly in the USA, where, for many years, 2.4 million units have been recommended by the Public Health Service for single-session therapy for early syphilis (6).

A single intramuscular injection of 300 000 units of benzathine penicillin G produces a serum penicillin concentration of 0.03 unit/ml for about 7 days. (The same dose of PAM does so for 3–4 days.) A single intramuscular injection of 2.4 million units of benzathine penicillin G ensures an effective penicillinaemia for 3–4 weeks. The percentage of patients in whom unsatisfactory serum levels are achieved in controlled studies is very small. For example, after an intramuscular injection of 1.2 million units, less than 0.5% of patients exhibited non-measurable penicillin levels after 1 week (7).

5.1.2 Treatment with antibiotics other than penicillin (see also section 5.2.2)

Not only penicillin, but most other antibiotics except for the aminoglycoside group (streptomycin, gentamicin) are active against *T. pallidum*—in particular, the cephalosporins (including cefaloridine), the tetracyclines, the macrolides (erythromycin, carbomycin, spiramycin), and chloramphenicol. None of these has been thoroughly evaluated in humans. Some antibiotics have been tested suc-
cessfully in experimental syphilis in the rabbit. Treponemicidal levels in rabbits vary from antibiotic to antibiotic. Rigorously controlled evaluations of these and newer antibiotics in the treatment of syphilis in humans are needed.

Some of these antibiotics are required for patients considered to be allergic to penicillin. Since basic data concerning their use in man is imprecise and they are less effective than penicillin, longer treatment schedules are required and a careful follow-up is necessary.

On the basis of cost-effectiveness and low incidence of side-effects, tetracycline hydrochloride or erythromycin (not the estolate) are to be preferred.

5.1.3 Approved minimum standards of therapy

Despite the efforts made to establish standard schedules of treatment by WHO and others, it is evident that many variations have been used (8) for various reasons, including lack of complaints on the part of patients and ignorance or individualistic attitudes on the part of physicians. The desirability of defining agreed minimum standards of treatment and making them widely known is self-evident.

5.1.4 Recommendations

1. Since PAM is no longer readily available in many countries, the following new guidelines for the treatment of syphilis should be adopted. Physicians should be cautioned never to use less than the recommended dosages.

2. For the treatment of early syphilis (i.e., primary, secondary, and latent infections of not more than two years' duration) these are:
   —Benzathine penicillin G, 2.4 million units in a single session by intramuscular injection (this offers the advantage of treatment being completed at one visit),
   OR
   —Aqueous procaine penicillin G, 600 000 units daily by intramuscular injection for 10 consecutive days.

3. The treatment for patients with early syphilis who are allergic to penicillin should be:
   —Tetracycline hydrochloride, 500 mg 4 times daily by mouth for 15 days. (Food, notably some dairy products, salts of calcium, aluminium and magnesium, and oral iron preparations interfere with absorption. Oral forms of tetracycline should therefore be given
1 hour before or 2 hours after meals. All forms of tetracycline are therapeutically effective when given in pharmacologically equivalent doses. Some preparations (e.g., doxycycline) offer certain advantages in respect of gastrointestinal absorption and tolerance but are more costly.)

OR

—Erythromycin (not the estolate), 500 mg 4 times daily by mouth for 15 days.

5.2 Treatment of late syphilis

5.2.1 Treatment with penicillin

(a) Basic data

Late acquired disease includes latent syphilis of more than 2 years' duration (including latent syphilis of indeterminate duration), late benign (gummatous) syphilis, cardiovascular syphilis, and neurosyphilis.

The same pharmacological principles apply to late syphilis as to the early stages. Their application ensures arrest of the pathological process.

(b) Criteria of “cure”

Clinical “cure” has to be distinguished from microbiological cure, i.e., the elimination of every single treponeme. Some studies have demonstrated spiral organisms in the cerebrospinal fluid, the aqueous humour, and the lymph nodes, following treatment of late infection. The full extent and significance of these findings require further study (see section 7).

Determining clinical “cure” is no less difficult, mainly because some 60% of untreated syphilitics undergo spontaneous “cure” or never develop late symptoms or signs. Over the last 30–40 years the percentage has risen, because of the number of syphilitics receiving treponemicidal drugs for a wide variety of nonsyphilitic conditions. There are few published reports that define what constitutes clinical “cure” in late syphilis. In many cases, one can say no more than that the patient has been “adequately treated”.

(c) Late latent and late benign syphilis

Penicillin forms an excellent basis for the therapy of these forms of late syphilis. Adequate treatment of late latent syphilis (occurring
more than 2 years after infection) results in arrest of the disease so that tertiary manifestations are prevented.

Benign gummatous late syphilis is now very rare, and treatment with penicillin results in rapid and complete healing of the lesions.

(d) Cardiovascular syphilis

No satisfactory controlled investigation of the efficacy of any form of penicillin in the treatment of cardiovascular syphilis has been undertaken. There is a general impression that there is a significant subjective improvement in the condition of patients following therapy, but, once symptoms occur, penicillin may have little or no obvious effect.

A raised erythrocyte sedimentation rate may fall with antibiotic treatment, and sometimes anginal pains may improve. But these pains can worsen, and further expansion of the thoracic aorta may occur in spite of therapy. The result may be a worsening of the aortic incompetence with secondary effects on cardiac sufficiency.

In addition to penicillin treatment, patients with aortic incompetence, angina of effort, and aneurysms of the aorta should have full assessment by a cardiologist and cardiac surgeon to determine whether valve replacement, coronary artery surgery, or removal of an aneurysm and replacement with a graft is indicated. The results of surgical procedures, even in elderly subjects, have improved greatly in recent years.

(e) Neurosyphilis

Treatment with penicillin is the method of choice in all forms of neurosyphilis, and the results can be judged by a reversal of abnormalities in the cerebrospinal fluid and in some cases by clinical improvement. As in cardiovascular syphilis, procaine penicillin G schedules have been commonly used.

A survey of experience with over 6000 cases of neurosyphilis (8) has shown the very favourable effect of treatment with penicillin of various types. Schedules with doses totalling more than 5 million units seem to be more effective than those involving lower doses. Asymptomatic neurosyphilis and meningeovascular syphilis respond dramatically, but the clinical response in general paralysis and tabes dorsalis is inversely related to the severity of the symptoms and the duration of the disease (9). Cases of optic atrophy and nerve deafness may progress regardless of antibiotic therapy. Neurological damage due to impaired neurons is permanent.
Repeated posttreatment cerebrospinal fluid examinations are essential if "cure" is to be declared.

Most of the persistent treponemes found after treatment have been detected in the cerebrospinal fluid and aqueous humour (10). The penetration of penicillin into these fluids is poor, and that of erythromycin even poorer.

Greater penetration and a higher, more prolonged concentration of penicillin in the cerebrospinal fluid and aqueous humour may be attainable by using high doses of crystalline penicillin G plus probenecid, or ampicillin plus probenecid. Whether higher or more prolonged levels would result in the elimination of the organisms and influence the outcome of treatment is unknown.

It is generally agreed that the optimum treatment schedules are less well established for all forms of late syphilis than for early syphilis, and that higher doses are required in the case of late syphilis.

The use of benzathine penicillin G in the treatment of neurosyphilis (and cardiovascular syphilis) is not yet well established. In more than one study it has not been possible to demonstrate penicillin in the spinal fluid after the usual dosage (11, 12). Basic data on the absorption and distribution of the antibiotic in the body at various dosages and body weights are inadequate.

Aqueous procaine penicillin G has given good results in active neurosyphilis, as in other forms of syphilis. It is likely that penetration into the cerebrospinal fluid is sufficient, at least if there are inflammatory changes. Certainly, after many years' use of procaine penicillin G for the treatment of all stages of syphilis, there would be a high incidence of late complications if treponemes commonly survived such treatment and caused late symptomatic syphilis, including neurosyphilis. This has not occurred.

5.2.2 Alternatives to penicillin in late syphilis (see also section 5.1.2)

For those allergic to penicillin, the alternatives are tetracycline and erythromycin, both of which are less effective than penicillin.

Doxycycline, 300 mg given orally once daily for 15 days, has been suggested for the treatment of asymptomatic late syphilis. A 21-day course for symptomatic late syphilis has been suggested (E. M. C. Dunlop, personal communication). This antibiotic is fully absorbed from the gut and its absorption is not impaired significantly by milk or milk products, but it is expensive.
Cefaloridine, 1 g twice daily for 21 days, is also effective in “complicated syphilis” (E. M. C. Dunlop, personal communication) but there may be cross-sensitivity with penicillin; it should never be given if there is any history of penicillin anaphylaxis, and its use should be considered only in exceptional circumstances. Some other antibiotics have marked treponemicidal activity, but experience with them is totally inadequate.

5.2.3 Herxheimer reaction in syphilis

The febrile Jarisch-Herxheimer reaction is observed in 50–80% of patients with early syphilis following the initiation of treatment with a treponemicidal drug. It is seldom serious and vanishes after 12–48 hours. In neurosyphilis, focal reactions have been reported, e.g., psychotic episodes following the initiation of treatment with penicillin or, less commonly, with tetracycline. The Herxheimer reaction in cardiovascular syphilis carries the risk of ostial oedema, coronary occlusion, or rupture of an aneurysm.

The mechanism of the Herxheimer reaction remains unknown. Sudden lysis of the killed treponemes is believed to be the essential cause. Small doses of an antibiotic will not prevent the reaction, though steroids may do so. Some physicians recommend short courses of steroids prior to antibiotic treatment in cases of cardiovascular syphilis and neurosyphilis. This applies particularly in cases of paresis with a raised cell count and protein content in the cerebrospinal fluid, in cases of optic atrophy, and in nerve deafness. There is, however, no firm scientific evidence to justify this procedure.

Steroids are also given in the longer-term treatment of optic atrophy. They may also be used in eighth-nerve deafness, sometimes with noticeable improvement of hearing. The pathological process, the persistency or absence of spiral organisms in the endolymph, and the optimum treatment are aspects of this condition that are poorly understood.

5.2.4 Recommended schedules of treatment for late syphilis

1. It should be emphasized that antibiotic treatment is less well established for late syphilis than it is for early syphilis. In general, late syphilis requires longer therapy.

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1 Cross-sensitivity exists in approximately 30% of patients allergic to penicillin but only 10–14% will exhibit clinical signs and symptoms after exposure (13).
2. In late latent syphilis of more than 2 years’ duration and late benign syphilis, aqueous procaine penicillin G, 600,000 units, should be given daily by intramuscular injection for 15 days. For cardiovascular syphilis and neurosyphilis, the treatment time should be extended to 20 days.

3. An alternative treatment is benzathine penicillin G, 2.4 million units weekly for 3 successive weeks. It is preferable to avoid such treatment in cases of cardiovascular syphilis and/or neurosyphilis.

4. Patients with any form of late syphilis who are allergic to penicillin should receive either: tetracycline hydrochloride, 500 mg 4 times daily by mouth for 30 days, or erythromycin (not the estolate), 500 mg 4 times daily by mouth for 30 days.

5. An examination of the cerebrospinal fluid is mandatory in patients with symptomatic neurosyphilis, necessary in all patients with

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<th>Table 5. Penicillin-based treatment schedules for venereal syphilis</th>
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<tr>
<td><strong>Benzathine penicillin G</strong></td>
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<td>Early syphilis (primary, secondary, early latent, i.e., of not more than 2 years duration)</td>
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<td>Cardiovascular syphilis and neurosyphilis</td>
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<th>Table 6. Treatment schedules for patients with venereal syphilis who are allergic to penicillin</th>
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<td><strong>Tetracycline hydrochloride (500 mg by mouth, 4 times daily)</strong></td>
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* Not the estolate.
syphilis of more than 2 years' duration (to exclude asymptomatic neurosyphilis), and essential in follow-up patients treated for neurosyphilis.

Recommended treatment schedules for venereal syphilis are summarized in Tables 5 and 6.

5.3 Diagnosis and management of syphilis in pregnancy

Pregnant women should be regarded as a separate group requiring close surveillance, especially to identify possible reinfection after treatment has been given. Infection is more prevalent in the multiparous.

5.3.1 Patient management

All women in each and every pregnancy should have serological screening for syphilis at their first antenatal visit. In women (or their partners) suspected of being “high-risk” subjects, the test(s) should be repeated in the third trimester. Seroreactive patients should have a history taken, be physically examined, and have a repeat blood specimen submitted for confirmatory VDRL or RPR testing, for TPHA testing, and, if indicated, for FTA-ABS testing. A quantitated non-treponemal test (e.g., the VDRL test) should be requested.

If the confirmatory test is negative, the tests should be repeated within 4 weeks. If there is clinical or confirmatory serological evidence of syphilis, or the disease cannot be excluded with reasonable certainty, the patient should be given the recommended treatment schedule for syphilis in pregnancy (see below).

If, however, there is good documentary evidence of adequate treatment being given in the past, the patient need not be re-treated unless there is evidence of recurrence (e.g., darkfield positive lesions or a 4-fold rise of serological titre, or recent known sexual contact with someone with infectious syphilis).

In some areas a diagnosis of past or present nonvenereal treponematoses may have to be considered.

5.3.2 Recommendations for therapy

1. Pregnant patients at all stages of pregnancy, who are not allergic to penicillin, should be treated with penicillin in the dosage schedules
recommended for the treatment of nonpregnant patients at a similar stage of the disease.

2. Patients at all stages of pregnancy who are allergic to penicillin should receive erythromycin (not the estolate) in the dosage appropriate for the stage of the disease, as recommended for nonpregnant patients.

(Although the erythromycin schedules appear safe for both mother and fetus, their efficacy is not well established and assessment of penicillin allergy is therefore important before using this antibiotic. Erythromycin estolate and the tetracyclines are not recommended for syphilitic infections in pregnant women because of potential toxic effects on mother and/or child.)

3. Following treatment, quantitated serological tests using nontreponemal antigens should be performed at monthly intervals until delivery, re-treatment being undertaken if there is evidence of reinfection or serological relapse. Thereafter, the follow-up of the mother is as for nonpregnant patients.

4. Tetracycline should not be used.

5.4 Treatment of congenital syphilis

5.4.1 Objectives

The ultimate aim in treating both early and late congenital syphilis is to cure the patient clinically, serologically, and biologically in the shortest period of time. For this, penicillin has proved its efficacy, but the optimum dose and the most suitable type of penicillin have yet to be determined. In this context, the shortcomings of benzathine penicillin G in the treatment of neurosyphilis have already been mentioned. As crystalline and aqueous procaine penicillin G can usually be safely given to neonates without the risk of a serious allergic reaction, other antibiotics that are treponemical have no place in the treatment of early congenital syphilis.

5.4.2 Guidelines to management

Congenital syphilis may occur if the expectant mother has syphilis, but this risk is minimal if she has had penicillin treatment during pregnancy. All infants of seropositive mothers adequately treated before or during pregnancy should be examined at birth and at monthly intervals for 3 months, that is, until serological tests are con-
firmed as negative and remain so. Any antibody carried over from mother to baby usually disappears within a month of birth. Treatment for congenital syphilis will be necessary only if there is a rise or persistence of serological titre and/or clinical or radiological signs of disease.

Infected babies of untreated syphilitic mothers are frequently asymptomatic at birth and may be seronegative if the mother was infected late in pregnancy. Infants should be treated at birth: (a) if the treatment of the mother was inadequate or is unknown; (b) if a drug other than penicillin (e.g., erythromycin) was used; or (c) if clinical and serological follow-up of the infant cannot be ensured.

5.4.3 Recommendations for treatment

1. Of the various schedules in use, those recommended by the United States Public Health Service (6) were adopted and adapted. The Scientific Group recommended:

(a) for the treatment of early congenital syphilis (up to 2 years of age) in infants with abnormal cerebrospinal fluid, crystalline penicillin G, 50,000 units/kg body weight intramuscularly or intravenously in 2 divided doses daily for a minimum period of 10 days, or aqueous procaine penicillin G, 50,000 units/kg intramuscularly in a single daily dose for 10 days;

(b) in infants with normal cerebrospinal fluid, aqueous procaine penicillin in the doses just stated, or benzathine penicillin G, 50,000 units/kg intramuscularly as a one-session treatment, is recommended.

Some workers treat all infants with congenital syphilis as if the cerebrospinal fluid findings were always positive.

2. In difficult circumstances, e.g., when no follow-up is possible, aqueous procaine penicillin or benzathine penicillin G in the doses stated may be given. (A course started with one form of penicillin can be completed with another, if circumstances so dictate.)

3. Antibiotics other than penicillin (e.g., tetracycline or erythromycin) are not recommended for neonatal congenital syphilis.

4. For congenital syphilis of 2 or more years' duration, the dosage should not exceed that used for late acquired syphilis.

5. After the neonatal period, the dosage of erythromycin or tetracycline given to those allergic to penicillin should not exceed that given in acquired syphilis of more than 2 years' duration. On no account should tetracycline be given to children under 8 years of age.
5.4.4 Results of treatment

Early congenital syphilis, like early acquired syphilis, responds well both clinically and serologically to adequate doses of penicillin. In seriously ill children with extensive mucous membrane and skin lesions and visceral and bone involvement, full recovery may be slow. Children in a poor nutritional condition may succumb to intercurrent infections, e.g., pneumonia. Admission to hospital is therefore usually routine.

5.5 Recommendations for follow-up of patients treated for syphilis, all stages

1. The follow-up of patients treated for early syphilis should be based on available medical services and resources. The clinical condition of the patient should be assessed and attempts made to detect reinfection during the first year after therapy. As a minimum, patients with early syphilis treated with appropriate doses and preparations of penicillin G should be evaluated clinically and serologically after 3 months to assess the results of therapy. Experience has shown that reinfections are most likely during the first year after therapy. A second evaluation should be performed 6–12 months after therapy to reassess the condition of the patient and detect possible reinfection. Patients who are treated with antibiotics other than penicillin should be followed up more frequently.

2. All patients with cardiovascular syphilis and neurosyphilis should be followed up for many years. The follow-up should include clinical, serological, cerebrospinal fluid, and, where necessary, radiological examinations based on the clinician’s individual assessment of the patient’s condition and evaluation of the illness.

3. At all stages of the disease, re-treatment should be considered when: (a) clinical signs or symptoms of active syphilis persist or recur; (b) there is a sustained 4-fold increase in the titre of a nontreponemal test; (c) an initially high titre nontreponemal test (e.g., VDRL 1:8 or above) persists for a year.

4. There should be an examination of the cerebrospinal fluid before re-treatment, unless reinfection and a diagnosis of early syphilis can be established.

5. Patients should be re-treated with the schedules recommended for syphilis of more than 2 years’ duration. In general, only one retreatment course is indicated because adequately treated patients may maintain stable, low titres in nontreponemal tests.
5.6 Contact treatment

5.6.1 Management

The Group emphasized that the management of a case of early syphilis requires not only the treatment of the patient but also the examination and treatment of all recent sexual contacts.

The term "epidemiological treatment" has often been used for the treatment of such contacts. The term "contact treatment" is more accurate and appropriate.

5.6.2 Recommendations

1. Treatment of individuals with syphilis should be considered incomplete until their current sexual contacts have been fully investigated. It is particularly important to investigate the sexual partners of pregnant women. Such investigations are the direct responsibility of the clinician (see also page 54).

2. Every effort should be made to establish a diagnosis in all contacts. Undiagnosed contacts who have been exposed to infectious syphilis within the preceding 3 months should be promptly treated as for early syphilis.

5.7 Penicillin reactions

5.7.1 Incidence of penicillin reactions

Fortunately, the side-effects of antitreponemal drugs are few. Accidental deaths following treatment are very rare and mainly due to anaphylactic shock reaction to penicillin. Besides allergic reactions, a wide spectrum of side-effects can occur, such as pseudo-allergic skin reactions, the Jarisch-Herxheimer reaction, and the Hoigné reaction (acute psychotic symptoms from the procaine in procaine penicillin).

The frequency of penicillin reactions in venereal disease patients is generally low. Data collected on over 74,000 cases before 1964 showed an incidence of less than 1% after a single injection, and of 6.6–10.2% after multiple injections. From a survey of 858,024 venereal disease patients treated with penicillin, it is estimated that there was only 1 fatal case per 78,002 treated patients (14).
5.7.2 Mechanisms of allergic reactions

(a) Allergic reactions to antibiotics

Specific allergic sensitization by drugs is produced by any of four mechanisms (15). These include: Type I, in which anaphylactic sensitivity is mediated by specific reagin antibodies in the IgE class, which may produce urticaria, Quincke oedema, asthma, or anaphylactic shock; type II, in which antibodies of the IgM or IgG class may produce cytotoxic immunoreactions such as leukopenia, thrombopenia, and erythrocytopenia; and type III, in which antibody-antigen immunocomplexes may cause serum sickness, purpura, etc. These three types, due to humoral antibodies, occur soon after application of the drug, i.e., type I after some minutes, and types II and III after some hours. Type IV is a cell-mediated reaction by specific, sensitized T-lymphocytes of the tuberculin or eczema type, which may occur 24–72 hours after drug application.

Penicillin is a hapten which must combine with proteins to become antigenic (16). The entire molecule, or only a metabolized part of it, such as the major antigen (penicilloyl polylysine) or minor metabolites, may be active. The allergic sensitization occurs especially in predisposed patients with a history of other allergic diseases such as atopic dermatitis, allergic rhinitis, or bronchial asthma, or in patients who have had previous treatment with penicillin.

(b) Prevention of penicillin reactions

(i) Taking a careful history

For the prevention of allergic reactions, it is important to take a careful history regarding atopic dermatitis, rhinitis, and asthma, as well as earlier reactions to penicillin or to other antibiotics or antigens. If there is a positive history involving an antibiotic proposed for treatment, cutaneous or other tests should be considered, if available. The following possibilities exist: (1) skin tests, for which highly trained, skilled personnel are required; (2) haemagglutination tests; and (3) tests with lymphocytes. The alternative of using another antibiotic is commonly chosen.

(ii) Skin tests

In cases of high allergy, skin tests may elicit a shock reaction. It is therefore wise to begin with small quantities and to choose the least dangerous intracutaneous method, such as the prick- or scratch-test,
followed, when negative, by intracutaneous tests. Penicilloyl polylysine (PPL) is the material in common use. The radioallergo-absorbent (RAST) test is carried out \textit{in vitro}. Like the PPL it detects penicillin IgE antibodies and may give false negative results (17).

(iii) \textit{Haemagglutination tests}

Haemagglutination tests measure IgG and IgM, but are less important for allergic reactions.

(iv) \textit{Tests with lymphocytes}

The lymphocyte transformation test (LTT) has a reactivity similar to that of skin tests with penicillin-G derivatives.

Even when the above-mentioned tests are negative, \textit{it cannot be concluded with absolute certainty that penicillin sensitization is indeed absent}. Therefore, if penicillin is used in persons with positive histories and negative skin tests, it is advisable to observe the patient for at least 15–30 minutes after the injection and to have an emergency kit at hand for treatment. Many physicians use an alternative antibiotic rather than risk a reaction.

5.8 Management of nonvenereal treponematoses

5.8.1 \textit{Requirements for a renewed offensive against the nonvenereal treponematoses}

The difficulties of obtaining supplies of PAM and the widespread availability and adequacy of benzathine penicillin G make the latter the drug of first choice. In preparing for further campaigns against the nonvenereal treponematoses, the theoretical possibility of an increased prevalence of penicillin allergy in the 1980s as compared to 20–30 years ago has to be considered, even though it is expected that such allergy will still be rare. In order to treat the nonvenereal treponematoses in patients allergic to penicillin, alternative modes of therapy must be evaluated.

There is also the possibility of the selection of penicillin-resistant bacteria (see section 6.3.1). Also, although penicillin-resistant treponemes have not emerged, there is no certainty that they will not do so in the future. This possibility makes it important to control endemic treponematoses in remote areas as soon as possible, that is, while the available antibiotics are still highly effective.
The Scientific Group endorsed the principles previously outlined for the WHO-assisted campaigns regarding the application of treatment based on prevalence. It saw no justification, however, for giving half doses to contacts, as previously recommended. Where the prevalence of clinically active cases is over 10%, total mass treatment is given: that is, the entire population receives the recommended treatment. Where the prevalence is 5–10%, patients and their contacts receive full doses and juvenile mass treatment is carried out, i.e., all children are given doses according to age (Table 7). Where the prevalence is under 5%, patients, as well as household and other obvious contacts, should be given the full recommended doses (selective mass treatment).

<table>
<thead>
<tr>
<th>Schedule for treatment of the nonvenereal treponematoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (million units of benzathine penicillin G)</td>
</tr>
<tr>
<td>patients</td>
</tr>
<tr>
<td>under 10 years</td>
</tr>
<tr>
<td>patients 10 years and over</td>
</tr>
<tr>
<td>Early and late active cases</td>
</tr>
<tr>
<td>Latent cases and contacts</td>
</tr>
<tr>
<td>0.6</td>
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<tr>
<td>1.2</td>
</tr>
</tbody>
</table>

5.8.2 Recommendations

1. Benzathine penicillin G should replace PAM in the treatment campaigns against nonvenereal treponematoses.

2. The doses for latent cases and contacts should be increased to match the dose for active cases.

3. The larger doses should be given at an earlier age, i.e., from the age of 10 years (Table 7).

REFERENCES

6. CONTROL ASPECTS

6.1 Objectives

Programmes for the control of syphilis and other treponematoses have two separate and not necessarily related objectives. The first is to interrupt the transmission of disease. The second is to reduce the prevalence of sequelae of infection. For example, the incidence of congenital syphilis can be reduced through extensive antenatal serological screening and treatment programmes, although the incidence of infectious syphilis remains unchanged. On the other hand, interruption of transmission necessarily reduces the total sequelae of the disease.

6.2 Syphilis control

Control of syphilis is relatively simple and problem-free compared with that of some other sexually transmitted diseases. It is favoured by a combination of factors: (a) low-cost, readily available screening tests, (b) effective, simple, inexpensive therapy, (c) a long incuba-
tion period with a relatively low transmission rate, and (d) self-limiting symptomatic periods with long asymptomatic periods of presumably low infectivity.

6.2.1 Available strategies

The basic means of interrupting transmission and preventing sequelae include treatment services for patients and sexual contacts, supporting diagnostic laboratory services, contact tracing and field investigation, serological screening, epidemiological techniques, and education and training programmes. The appropriate mixture of strategies depends on the prevalence of the disease, the results of analyses of the local epidemiological pattern, and the availability of human and material resources.

(a) Primary health care services

The basic strategy for syphilis control involves the treatment of patients or suspected patients and their sexual partners with an effective, safe, relatively inexpensive antibiotic, i.e., penicillin. Thus syphilis is unlikely to be a major problem where the population has access to a competent health service.

Barriers to populations receiving health care severely limit attempts to interrupt disease transmission or prevent sequelae. These barriers include: (i) lack of services owing to financial restraints; (ii) services which are not accessible, e.g., with limited clinic hours, in a poor geographical location, etc.; (iii) services which are not acceptable, e.g., poorly staffed clinics with undignified, censorious, or punitive approaches, etc.; (iv) unaffordable services, e.g., private practitioners that are not available to lower socioeconomic groups; (v) failure of health workers and health administrators to appreciate the cost benefits of syphilis control measures applied at the primary health care level; (vi) failure of patients to cooperate in management policies.

The integration of diagnostic and therapeutic standards into primary health care systems and the removal of barriers to the utilization of such systems constitute a first step in syphilis control. The same principles apply in all settings regardless of the prevalence of the disease in the population.

(b) Supporting diagnostic laboratory services

The introduction of laboratory techniques into primary health care systems depends on the availability of resources to support the mi-
croscope and serological techniques described in section 4. Without quality control, proficiency testing, and general evaluation programmes, these laboratory services will degenerate and be a waste of time and valuable resources.

(c) Contact tracing

Contact tracing is the term used for the various techniques by which the sexual partners of diagnosed patients are identified, located, investigated, and treated. It is useful to distinguish the identification of current sexual contacts, e.g., spouses and other frequent or stable sex partners, from the more difficult process of tracing primary sources and the spread of infection in occasional or unknown partners. The former is the clinician’s direct responsibility in all settings since it is an indispensable component of the effective management of the individual patient. The latter calls for a specialized outreach strategy requiring appropriately trained staff skilled at identifying sources and the spread of disease in chains of infection. Contact tracing is relatively expensive and is most useful where prevalence is low.

(d) Serological screening

The term “serological screening” denotes the mass screening of target populations. The aim is to separate a given population into those groups in which the probability of having syphilis is high and those in which it is low.

Other disease control measures, e.g., education, can also be focused on the high-risk or high-probability groups. To be an effective epidemiological and disease control tool, mass serological screening must achieve a high coverage of each selected subgroup of the population (1).

The decision to initiate mass screening programmes depends on the prevalence of syphilis, the need to identify high-risk groups, and the characteristics and cost of the screening tests themselves.

A decrease in disease prevalence does not necessarily or immediately follow the implementation of a mass screening programme, since people can become infected at any time, whether they have been screened or not.

Even when the incidence of syphilis has been reduced to an apparently irreducible minimum, i.e., control has been established, screening programmes need to be continued in order to monitor and maintain control.
The VDRL test is an excellent screening test for syphilis. It is cheap and simple, and its results are readily reproducible. Although it may be nonspecific in certain environments, its nonspecificity can be minimized by using a treponemal test (i.e., the TPHA test) concomitantly or sequentially.

(e) Mass treatment

When the prevalence of syphilis is found to be exceptionally high, e.g., among prisoners, certain homosexuals, or other selected high-risk groups, mass treatment may be warranted. The implementation of such an approach depends on an accurate assessment of the prevalence of the disease, the levels of transmission, and ability to implement the programme, e.g., to locate the individuals to be treated and obtain their consent.

(f) Education and training programmes

Three target groups are identifiable for education programmes specifically designed to alter knowledge, attitudes, and behaviour. These are, in order of priority:

(i) Health workers. Education programmes must be designed to provide health workers with appropriate technical skills (diagnosis, treatment, case management, interviewing, and statistical, epidemiological, and administrative techniques). In addition, teaching is essential to provide insight into how and to what extent the clinician’s own emotions and reactions affect patients and influence their relations with the health care service, their compliance with treatment and follow-up schedules, and their cooperation in contact-tracing procedures.

(ii) Patients. Patients require information about their medical condition and their role in transmitting the disease. This education is essential if each and every patient is to be motivated to participate in syphilis control, e.g., by referring their sexual contacts for evaluation and treatment.

(iii) General public. Educational programmes for the general public should receive relatively low priority. Their benefits for disease control are limited and uncertain, unless they are carefully designed for special target groups, e.g., homosexuals, adolescents, etc., and rigorously evaluated with regard to specific objectives.
6.2.2 Needs for syphilis control

Hindrances to the establishment of effective syphilis control programmes have to be removed. The needs are as follows:

(a) Epidemiological analysis is needed so that resources may be appropriately allocated. Measurements of current costs of syphilis and its sequelae should be included.

(b) Health care services dealing with syphilis control need to pay specific attention to populations at high risk. In some areas, for example, homosexuals present a major challenge. They may desire anonymity, change their partners frequently, and have many unknown contacts. Comprehensive strategies, including serological screening and ensuring good rapport with health workers, speedy and efficient care, and sound education, may need to be designed and deployed.

(c) The training of professional and paraprofessional personnel in the technical and logistical aspects of syphilis control is urgently needed.

(d) Directors of programmes need further training in the principles and application of available strategies. The high level of epidemiological and management expertise required is not generally found in clinical personnel. It is unreasonable to expect clinicians who have not been appropriately trained to apply all the philosophies, principles, and skills of active, broadly based, disease control programmes.

(e) Information concerning available control strategies, the indications for their use, and the details of their application in different settings needs to be widely distributed. This applies particularly to primary health care facilities.

(f) Each country needs at least one centre of excellence to provide the facilities for an effective control programme.

6.2.3 Recommendations for syphilis control

1. Guidelines should be established on: (a) the efficient epidemiological analysis of the extent of syphilis, (b) the logistics of syphilis control programmes, and (c) the indications for, and application of, various control strategies.

2. Three types of training course should be provided within syphilis control programmes, i.e., for clinicians, field workers, and managers
respectively. Support should be given to the provision of guidelines and materials for such courses.

3. Every country should be encouraged to establish a national forum to promulgate the latest information on syphilis control and provide support for national programmes. Such forums or groups should have had appropriate training and experience in the control of sexually transmitted diseases and establish liaison with appropriate governmental and nongovernmental organizations (including the International Union against Venereal Diseases and Treponematoses).

4. Countries with limited resources should be assisted in the development of appropriate clinical, laboratory, and treatment services in the area of primary health care in order to reduce the incidence of all forms of syphilis.

5. Each country should establish at least one centre of excellence in the control of sexually transmitted diseases. This centre should take responsibility for the supervision of clinical standards, laboratory techniques, training, epidemiological practices, and implementation of control programmes.

6.3 Control of nonvenereal treponematoses

6.3.1 General considerations

The traditional approach to yaws control (2) consisted of five phases:

(a) orientation and preliminary analysis of the problem,
(b) development of methodology,
(c) demonstration, survey, and training phase,
(d) expansion phase,
(e) consolidation phase.

This approach is still valid today and is equally applicable to the control of endemic syphilis. The categorical nature of an intensive yaws control programme makes it difficult to integrate into systems based on current concepts of primary health care. If specially trained teams are used, their aims should include turning over the responsibility for yaws surveillance in the consolidation phase to village health workers, schoolteachers, or other appropriate local staff.

Recent evaluations of yaws prevalence and control programmes in Ghana, Ivory Coast, and Togo revealed a number of common problems. The first is the need for the accurate collection and reporting of
cases, using simple, standard criteria for diagnosis. The second is the lack of a sampling technique permitting the distribution of yaws to be determined by a simple and relatively inexpensive method. A third problem is that of deficiencies in current yaws control efforts, including:

(a) low population coverage owing to a combination of inadequate planning, deficient public notification or education, lack of accurate census data, public apathy, and failure to treat contacts of treated cases;

(b) failure to coordinate yaws control efforts in adjoining countries or areas with the aim of creating an ever larger yaws-free area, the result being that treated populations are immediately re-exposed to yaws imported from untreated populations in neighbouring areas;

(c) assigning yaws control tasks to health teams untrained in yaws control, such as vaccination, cholera control, or malaria control teams;

(d) failure to recognize the disease, owing to lack of experience on the part of health workers in primary health care areas where prevalence has been low for many years (many of the clinical presentations now seem less severe than in pictures in the available books).

These problems call for certain modifications and innovations in recommended control policies so that they can be adapted to the resources and health priorities of individual countries.

It is possible that mass penicillin treatment campaigns today might adversely affect the antibiotic resistance of certain bacterial pathogens such as the gonococci, meningococci, and *Haemophilus* and *Gardnerella* species. These organisms are highly prevalent in West Africa, for example, and the selective pressure exercised by the widespread use of long-acting penicillin could result in epidemics of penicillinase-producing *Neisseria gonorrhoeae* and penicillin-resistant meningococci.

Another potential consequence of yaws control is an increase in venereal syphilis. There is considerable experimental and epidemiological evidence (3) that yaws provides partial immunity to venereal syphilis. The near-eradication of yaws in Haiti has been followed by a disconcertingly high prevalence of venereal syphilis. This situation, however, calls for improved control of venereal syphilis, rather than any relaxation of efforts to eradicate yaws or other nonvenereal treponematoses.

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1 **Medina, R.** Unpublished WHO document WHO/VDI/RES/63.64.
Mass treatment programmes would be more difficult than in the past, owing to greater population mobility and might not be warranted by the current prevalence in some areas.

6.3.2 Needs

1. Guidelines for control based on appropriate modifications of programmes that were successful in the past but may not be appropriate at present, e.g., mass treatment campaigns.
2. Guidelines for more selective screening around infected cases.
3. Training of staff to implement the modified programmes.

6.3.3 Recommendations

1. The publication of new, simplified, guidelines for the planning and implementation of control programmes should be treated as a priority.
2. Health authorities in the tropics should be encouraged to carry out basic epidemiological investigations of the nonvenereal treponematoses in areas known or suspected to be affected.
3. National and regional efforts to control nonvenereal treponematoses should be encouraged, coordinated, and publicized with emphasis on the cost-effectiveness of early implementation.
4. Appropriate strategies for controlling nonvenereal treponematoses and for maintaining such control at all levels of the health care system should be clearly formulated, with particular reference to the role of primary health care services.
5. Early action should be taken to prevent the increase in late yaws cases expected as a result of the current epidemic of early cases.

REFERENCES

7. RESEARCH ASPECTS

7.1 Investigation of *T. pallidum*

7.1.1 Cultivation of *T. pallidum*

Long-term hopes for immunoprophylaxis make cultivation of *T. pallidum* a top priority. In the past decade there has been a marked increase in efforts to cultivate pathogenic treponemes *in vitro*, either alone or with mammalian cells of various types. These investigations have shown the conditions that will permit prolonged *in vitro* survival of treponemes, with retention of their pathogenicity for animals (1). As yet there is no convincing evidence of the propagation of treponemes outside the mammalian host.

7.1.2 Survival of *T. pallidum* in cell cultures

Pathogenic treponemes (but not cultivable nonpathogens) attach themselves to mammalian cells in culture. This cell attachment occurs in an orderly fashion, by the tips of the treponemes only. Once attached, the organisms remain so for prolonged periods of time. Not all the treponemes in culture associate themselves with cells in this fashion. It has been repeatedly observed that treponemes attached to cells are more vigorously motile, and retain their motility much longer, than the organisms that are not cell-attached. This observation has been interpreted as possible evidence for nutritional parasitism by treponemes. If so, this would preclude the eventual cultivation of treponemes in a cell-free system (2).

7.1.3 Metabolic capabilities of *T. pallidum*

Whereas efforts at *in vitro* culture have been disappointing, studies of the metabolic capabilities of treponemes have contributed to the modest successes recorded with the prolonged *in vitro* survival of these microorganisms in culture. It is now evident that *Treponema pallidum* is a micro-aerophilic bacterium and not the strict anaerobe it was previously thought to be (3). *T. pallidum* has been shown, quite convincingly, to utilize oxygen as a terminal electron receptor by an aerobic energy-yielding pathway (4). The manner in which it utilizes glucose has been elucidated, and evidence for other metabolic capabilities has been found (5). The studies have failed to reveal any
metabolic handicaps and, though not conclusive, offer some hope of the eventual cultivation of treponemes in a cell-free environment. In this respect, they contrast with the tissue culture studies.

7.1.4 Biochemical investigations

The use of new techniques has permitted, to some extent, the chemical dissection of treponemes at the molecular level (6). This has made it possible to identify certain treponemal components, such as those shared with nonpathogenic organisms and those related to cell attachment, as described above. While this is only a modest beginning, it clearly reveals that components of significance can be isolated and identified.

7.1.5 Defining antigens

To date, little information is available on the treponemal components of immunological significance. Research in this field is extremely important since it might greatly facilitate recognition of the disease by permitting the investigation of more sensitive methods for detecting antibodies.

7.1.6 Genetic aspects

Once components of particular interest have been identified, they may be produced in quantity through genetic engineering, i.e., by inserting the appropriate treponemal genetic information into a readily cultivable bacterium. It is possible that this could have practical value for both the development of more specific diagnostic tools and the production of protective immunogens.

7.1.7 Recommendations

Studies should be undertaken:

(a) to culture any of the pathogenic treponemes in vitro;
(b) to isolate, identify, and utilize individual treponemal components of immunological significance. The studies should include not only standard immunochemical studies, but also "genetic engineering" projects aimed at the productive insertion of treponemal genetic information into a readily cultivable microorganism, e.g., *E. coli*.
7.2 Immunity

7.2.1 Cellular immunity

The role of cellular immunity in treponemal infection has attracted much interest in the past decade. Studies in both man and experimental animals have yielded a wealth of conflicting information. The hard evidence indicates that cellular immunity plays a major role in treponemal infection.

7.2.2 Humoral immunity

Among the many new technical advances in the biological sciences are those permitting markedly increased sensitivity in the detection of immunoglobulins (7, 8, 9). These have made it possible to develop more sensitive and better quantitated serological techniques and have been applied to some extent in the serology of syphilis. Current studies suggest that more sensitive and more specific diagnostic procedures may be available in the near future.

The value of the tests to identify T. pallidum-specific 19S (IgM) antibodies for the diagnosis of syphilis needs to be investigated further, with special emphasis on their possible ability to distinguish between active and inactive states of the disease (see section 4.3.8). The evidence available so far (10, 11) strongly suggests that IgM antibodies against T. pallidum are produced as long as the antigen is present in the host. This view is supported by the observation that IgM disappears within a few months after adequate treatment of early syphilis and within about one year after appropriate therapy of late infection. A longer persistence of IgM reactivity following effective treatment would appear to be highly improbable since IgM antibodies cannot be produced by memory cells.

7.2.3 Recommendations

1. Newer and more sensitive methods for detecting antibodies should be investigated with particular emphasis on procedures that permit quantitation and immunoglobulin identification. The aim is to develop tests suitable for routine laboratory use.

2. Studies should be encouraged to determine the value of the 19S IgM test on serum for the diagnosis of syphilitic infection, with special emphasis on its ability to distinguish between active and inactive disease and the associated need for treatment.
7.3 New parameters for the diagnosis of neurosyphilis by cerebrospinal fluid (CSF) examination

7.3.1 A new approach

The lack of a reliable indicator for recognition of central nervous system (CNS) involvement in syphilis has stimulated further investigation for a specific parameter. Preliminary results are available on the following methods for diagnosing CNS involvement (12) but further research is necessary:

(a) Albumin quotient

The albumin quotient = \( \frac{\text{CSF albumin (mg/dl)} \times 1000}{\text{serum albumin (mg/dl)}} \).

This quotient has been suggested as a means of defining the normality or degree of impairment of the blood/CSF barrier occasioned by inflammation. Normal values range between 3.0 and 8.0 depending on the age of the patient (13).

(b) IgG index

The IgG index = \( \frac{\text{IgG quotient}}{\text{albumin quotient}} \).

This indicates inflammation (syphilitic as well as nonsyphilitic) in the close vicinity of the CSF membrane. The IgG quotient is calculated by the formula \( \frac{\text{CSF IgG (mg/dl)} \times 1000}{\text{serum IgG (mg/dl)}} \) and is analogous to the albumin quotient (14).

(c) TPHA index

\( T. pallidum \)-specific IgG is indicated by the TPHA test. CSF-TPHA titre values above 2560 may be considered suggestive of active neurosyphilis.

TPHA test results may be misleading in cases where a severe breakdown of the blood/CSF barrier function is indicated by albumin quotient values 20–40 times above normal. In order to adjust for blood/CSF barrier permeability, a TPHA index \( \left( \frac{\text{CSF-TPHA titre}}{\text{albumin quotient}} \right) \) has been proposed. Its normal range is below 100, provided the albumin quotient is not extremely high (e.g., above 20–30).
(d) T. pallidum-specific immunoglobulins in the CSF

The occurrence of T. pallidum-specific IgM in the CSF is most probably indicative of neurosyphilis because the big IgM molecules cannot pass the intact (uninflamed) blood/CSF barrier. The presence of such IgM in the CSF is therefore most probably a result of syphilitic inflammation in and near the membranes associated with the CSF.

Little evidence is available on the occurrence of T. pallidum-specific IgA in the CSF. It has been shown to appear in neurosyphilis and might be of diagnostic as well as of pathogenic significance. The competitive inhibition of IgG by IgA may prevent stimulation of complement production and thus block an essential factor of the host defence.

7.3.2 Recommendation

It is recommended that studies be encouraged to evaluate the usefulness (i.e., sensitivity, specificity, predictive value) of indicator systems for T. pallidum-specific immunoglobulins and other parameters (e.g., albumin quotient, IgG index, TPHA index, and 19S IgM SPHA test) as means of detecting active CNS syphilis.

7.4 Clinical immune response

7.4.1 General

The pathogenic mechanisms responsible for the development and resolution of clinical signs are almost entirely unknown.

7.4.2 Recommendation

Studies should be encouraged into the pathogenic mechanisms responsible for the production and recession of treponemal lesions, with the development of immunoprotection against infection as the ultimate goal.

7.5 Treatment

7.5.1 General

The effectiveness of some antibiotics in the treatment of early as well as of late syphilis is not yet established. The list includes benzathine penicillin in neurosyphilis, as well as ampicillin, talampicillin,
cefaloridine and other cephalosporins, tetracyclines (particularly doxycycline), and macrolide antibiotics (erythromycin) in all stages of the disease. Retrospective as well as prospective studies should help to determine the value of these drugs in the therapy of syphilis as well as of nonvenereal treponematoses.

7.5.2 Recommendation

In view of the paucity of published information, WHO should encourage the collection and collation of retrospective and prospective data concerning the treatment of early and late syphilis with antibiotics other than crystalline and procaine penicillin.

7.6 Survival of *T. pallidum* after therapy

7.6.1 General considerations

Several authors have been able to detect *T. pallidum* in the cerebrospinal fluid, in the aqueous humour of the eye (15), in the perilymph of the inner ear, and in lymph nodes in human syphilis following adequate treatment. Some of these treponemes have been inoculated into rabbits and have produced typical lesions. Animal experiments also suggest that *T. pallidum* survives adequate penicillin treatment under certain circumstances. A critical evaluation of these reports, however, reduces the number of cases in which survival has been proved beyond doubt to very few. The penicillin sensitivity of the surviving treponemes has remained unchanged in all cases. The respective observations in humans may therefore be considered to indicate treatment failures, probably due to abnormal penicillin metabolism in the patients concerned ("quick penicillin excreters") rather than to penicillin resistance.

The number of cases reported, however, is not significant enough to suggest a change in the current treatment schedules. Careful clinical follow-up with serological and cerebrospinal fluid examination will indicate any need for re-treatment. Case reports of relapses should be published.

7.6.2 Recommendation

The question of surviving *T. pallidum* should be subjected to further investigations, particularly with regard to body fluids and lymph
nodes. The significance of the occurrence of \textit{T. pallidum} in the CSF and its probable influence on neurosyphilis needs special consideration.

7.7 Genital ulcers

The facilities for the differential diagnosis of various causes of genital sore are unsatisfactory in several countries. Field investigation involving the temporary use of high-standard laboratories may increase the possibilities for better diagnosis, treatment, and control measures in primary health care areas.

7.7.1 Recommendation

Field clinical studies, backed by sophisticated laboratory facilities, should be conducted to identify causes of genital sore.

REFERENCES

8. SUMMARY OF RECOMMENDATIONS

8.1 Epidemiological aspects

8.1.1 Syphilis

1. The following categories should be used in reporting cases of syphilis:
   (a) primary and secondary infections,
   (b) early latent infections,
   (c) late latent infections,
   (d) symptomatic late infections,
   (e) congenital infections in patients under 2 years of age,
   (f) congenital infections in patients 2 years of age or older.
   Early latent syphilis means asymptomatic seroreactive syphilis of not more than 2 years' duration.

2. This classification should be considered by WHO and relevant nongovernmental organizations, including the International Union Against Venereal Diseases and Treponematoses (IUVDT), and taken into account when the International Classification of Diseases is reviewed.

3. Incidence rates of early syphilis (the sum of primary, secondary, and early latent cases) should be collated:
   (a) by age group in years (under 10, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–49, 50 and over),
   (b) by sex (M/F),
   (c) by other parameters helping to distinguish the incidence in different social groups.

8.1.2 Endemic treponematoses

As a stimulus to the implementation of World Health Assembly resolution WHA31.58 on the control of nonvenereal treponematoses:

(a) Countries affected by nonvenereal treponematoses should determine the nature and extent of the problem (see section 8.5.2);

(b) WHO should publish annually the surveillance data on nonvenereal treponematoses reported by health administrations and obtained by special surveys;

(c) WHO should encourage the treatment, surveillance, and control of these diseases.
8.2 Clinical aspects

1. Improved teaching should have the highest priority, particular attention being given to congenital syphilis.
2. Serological examinations for syphilis should be routinely carried out on patients with neurological and psychiatric diseases. When the serological test is reactive, a cerebrospinal fluid examination should be made to confirm the diagnosis.
3. Syphilitic aortitis should be considered in all cases of abnormal X-ray findings of the aorta. A cerebrospinal fluid examination is advisable because concomitant neurosyphilis often occurs.
4. In view of the recrudescence of yaws in some areas and decreasing familiarity with the clinical picture, a new compact atlas of non-venereal treponematoses illustrating the common lesions in colour should be published.

8.3. Laboratory aspects

8.3.1 Microscopy tests

1. Darkfield microscopy should be the preferred diagnostic test for infectious treponemal disease.
2. The provision of darkfield condensers and light sources for existing microscopes should be encouraged. Where conventional microscopes are unsuitable, field microscopes should be considered.
3. Training programmes for laboratory personnel should include all skills essential to darkfield microscopy.

8.3.2 Serological tests

1. For screening and diagnostic purposes, two tests, one using a lipoidal antigen and the other a treponemal antigen, are the best choice.
2. In conditions of high prevalence and limited resources either the VDRL or RPR test should be used alone for screening.
3. The lipoidal test should be quantitated when reactive.
4. In parallel with the VDRL test, the TPHA test should be used to detect late treponemal disease.
5. The FTA-ABS test should be reserved as a confirmatory test for sera giving discrepant results in the initial tests.
6. The TPI test is no longer necessary as a confirmatory test for the treponematoses. It might be useful to maintain it in a few laboratories for research purposes.
8.3.3 Standardization of reagents and methods

1. The standardization of test reagents should be given the highest priority.
2. The RPR and other reagin tests should be standardized in terms of the VDRL titre.
3. "Automated" methods should be evaluated to produce results comparable to those obtained with the standard manual methods.
4. Governments should be encouraged to establish national reference laboratories with responsibility for monitoring laboratory performance.
5. An interchange of individual sera between laboratories for comparative testing should be encouraged, as should splitting specimens between laboratories.
6. Internationally acceptable pools of control sera should be established and made available to assist laboratories to check their levels of test proficiency.
7. Wherever possible, all reagents should be subjected to premarket assay by an independent authority.

8.3.4 Other diagnostic indicators

1. The cell count and the total protein content of the cerebrospinal fluid should be used as indicators of inflammations and of treatment response.
2. Research should be carried out to improve indicators of active syphilitic infection.

8.4 Treatment aspects

Physicians should be cautioned never to use less than the recommended dosages.

8.4.1 Treatment of early acquired syphilis (i.e., primary, secondary, and latent infections of not more than 2 years' duration)

(a) Benzathine penicillin G, 2.4 million units in a single intramuscular injection

OR

(b) Aqueous procaine penicillin G, 600 000 units daily by intramuscular injection for 10 consecutive days (total dose, 6.0 million units).
The treatment for patients with early syphilis who are allergic to penicillin should be:

(c) Tetracycline hydrochloride, 500 mg 4 times daily by mouth for 15 days

OR

(d) Erythromycin (not the estolate), 500 mg 4 times daily by mouth for 15 days.

(Although both of these antibiotics appear to be effective, they have been evaluated less extensively than penicillin.)

8.4.2 Treatment of late acquired syphilis

1. It should be emphasized that, for syphilis of more than 2 years’ duration, the optimum schedules of treatment are less well established than those for early syphilis. More prolonged therapy is indicated.

2. The following treatment should be given to patients with late latent syphilis, including latent syphilis of unknown duration, and late benign syphilis:

(a) Aqueous procaine penicillin G, 600 000 units daily by intramuscular injection for 15 days (total dose, 9.0 million units).

OR

(b) Benzathine penicillin G, 2.4 million units weekly for 3 successive weeks (total dose, 7.2 million units).

In the case of cardiovascular syphilis or neurosyphilis, it is preferable to avoid treatment (b) and to give treatment (a), extending the treatment time to 20 days (total dose, 12.0 million units).

3. The treatment of patients with any form of late syphilis who are allergic to penicillin should be:

(a) Tetracycline hydrochloride, 500 mg 4 times daily by mouth for 30 days

OR

(b) Erythromycin (not the estolate), 500 mg 4 times daily by mouth for 30 days.

4. An examination of the cerebrospinal fluid is mandatory in patients with symptomatic neurosyphilis, desirable in all patients with syphilis of more than 2 years’ duration (to exclude asymptomatic neurosyphilis), and particularly desirable in patients treated with regimes using alternative antibiotics other than penicillin.
Recommended schedules for venereal syphilis are summarized in Tables 5 and 6 (page 43).

8.4.3 Diagnosis and management of syphilis in pregnancy

1. Pregnant patients should be treated with penicillin in the dosage schedules recommended for the treatment of nonpregnant patients at a similar stage of the disease.

2. Patients allergic to penicillin should receive erythromycin (not the estolate) in the dosage appropriate to the stage of the disease, as recommended for nonpregnant patients.
   (Although the erythromycin schedules appear safe for both mother and fetus, their efficacy is not well established and it is therefore important to assess penicillin allergy before using this antibiotic. Erythromycin estolate and the tetracyclines are not recommended for syphilitic infections in pregnant women because of potential toxic effects on mother and/or child.)

3. Following treatment, quantitated serological tests using nontreponemal antigens should be performed monthly until delivery, re-treatment being undertaken if there is evidence of possible re-infection. Thereafter, the follow-up of the mother is as for non-pregnant women.

8.4.4 Treatment of congenital syphilis

1. Infants under 2 years of age: aqueous procaine penicillin G, 50,000 units/kg (150,000–300,000 units) should be given intramuscularly in a single daily dose for a minimum of 10 days

   OR

in circumstances when no follow-up is possible, benzathine penicillin G (50,000 units/kg) may be given intramuscularly in a single dose (a course started with one form of penicillin can be completed with another if circumstances so dictate). Published data on the efficacy of benzathine penicillin in congenital neurosyphilis are lacking. In cases of early congenital neurosyphilis, crystalline penicillin (50,000 units/kg body weight) daily in 2 divided doses intramuscularly is recommended as an alternative to aqueous procaine penicillin G. Antibiotics other than penicillin (e.g., tetracycline or erythromycin) are not recommended for neonatal congenital syphilis.

2. Children 2 years and over: the doses of penicillin should not exceed those used in late acquired syphilis of adults. In those allergic to
penicillin, the dosage of erythromycin or tetracycline should not exceed that given in acquired syphilis of more than 2 years' duration. *On no account* should tetracycline be given to children under 8 years of age.

8.4.5 *Follow-up of treated patients*

1. The follow-up of patients treated for early syphilis should be based on available medical services and resources. As a minimum, patients should be evaluated clinically and serologically after 3 months. A second evaluation should be performed 6–12 months after therapy. Patients treated with antibiotics other than penicillin should be followed up more frequently.

2. Patients with cardiovascular syphilis or neurosyphilis should be followed up for many years.

8.4.6 *Re-treatment*

1. The possibility of reinfection should always be considered when re-treating patients with early syphilis. An examination of the cerebrospinal fluid should be made before re-treatment unless reinfection and a diagnosis of early syphilis can be established.

2. In all stages of the disease, re-treatment should be considered when: *(a)* clinical signs or symptoms of active syphilis persist or recur; *(b)* there is a sustained 4-fold increase in the titre of a nontreponemal test; *(c)* an initially high-titre nontreponemal test (e.g., VDRL, 1:8 or above) persists for a year.

3. Patients should be re-treated with the schedules recommended for syphilis of more than 2 years' duration.

8.4.7 *Treatment of nonvenereal treponematoses (yaws, endemic syphilis, bejel, pinta)*

For early and late active cases in patients under 10 years of age 0.6 million units of benzathine penicillin G should be given, and for those in patients 10 years and over 1.2 million units. The same doses should be applied to latent cases and contacts (see Table 7, page 51).
8.5 Control aspects

8.5.1 Syphilis control

1. Practical guidelines should be established on (a) the efficient epidemiological analysis of the extent of syphilis, (b) the logistics of syphilis control programmes, and (c) the indications for, and application of, various control strategies.

2. Highest priority should be given to the prevention of congenital syphilis, which should be the first step in any control programme as it is relatively easy to implement and also very cost-effective.

3. Three types of training courses should be included in syphilis control programmes, i.e., for clinicians, field workers, and managers respectively.

4. All countries should be encouraged to establish a national forum or group to promulgate the latest information on syphilis control and provide support for national programmes.

5. Help with the development of clinical and laboratory services should be given to countries with limited resources.

6. Each country should establish at least one centre of excellence in the control of sexually transmitted diseases to take responsibility for the supervision of clinical standards, laboratory techniques, training activities, and epidemiological practices, and for monitoring the control programme.

8.5.2 Control of nonvenereal treponematoses

1. New and simplified guidelines for the planning and implementation of control programmes should be published.

2. Health authorities should be encouraged to carry out basic epidemiological investigations of the extent of the nonvenereal treponematoses in their territories.

3. National and regional efforts to control nonvenereal treponematoses should be encouraged, coordinated, and publicized.

4. Appropriate strategies for controlling nonvenereal treponematoses and for maintaining such control at all levels of the medical system, in the context of routine primary health care services, should be clearly formulated.
8.6 Research aspects

8.6.1 Culture of T. pallidum

Studies should be undertaken:
(a) to culture any of the pathogenic treponemes *in vitro*;
(b) to isolate, identify, and utilize, possibly by means of “genetic engineering”, individual treponemal components of immunological significance for improving serological test systems and enhancing vaccine development.
(c) To elucidate the nature of treponemal forms that have been found in body fluids and tissues following adequate penicillin treatment, keeping in mind the possible evolution of penicillin-resistant treponemes.

8.6.2 Tests for syphilis

1. New and more sensitive methods for detecting antibodies should be investigated, with particular emphasis on procedures that permit quantitation and/or immunoglobulin identification.
2. Studies should be encouraged on practical serological tests for the diagnosis of syphilitic infection, with special emphasis on their ability to distinguish active from inactive disease (and thus determine if treatment is needed). Test systems to identify *Treponema pallidum*-specific immunoglobulins and parameters of cerebrospinal fluid (e.g., albumin quotient, the IgG index, and the TPHA index) should be evaluated as a means of detecting active syphilis of the central nervous system.

8.6.3 Clinical

Further studies should be encouraged into the pathogenic mechanisms responsible for the production and recession of treponemal lesions, with the development of immunoprophylaxis against infection as the ultimate goal.

8.6.4 Treatment

In view of the paucity of published information and the reluctance of some clinicians to employ penicillin, considerably more data should
be obtained concerning the efficacy of antibiotics other than crystalline and aqueous procaine penicillin in the treatment of venereal and nonvenereal treponematoses.

8.6.5 *Field studies*

Field studies, backed by sophisticated laboratory facilities, should be conducted to identify the causes of genital ulcers and the associated symptomatology of such ulcers. The aim is to improve treatment strategies for these lesions at primary health care centres lacking laboratory support.
Recent reports:

No. 655 (1980) Resistance of vectors of disease to pesticides
Fifth report of the WHO Expert Committee on Vector Biology and Control (82 pages) ................................. 6.—

No. 656 (1981) Assessment of public health and social problems associated with the use of psychotropic drugs

Report of a WHO Scientific Group (76 pages) ......................... 5.—

No. 658 (1981) WHO Expert Committee on Biological Standardization
Thirty-first report (324 pages) ............................................. 21.—

No. 659 (1981) Wholesomeness of irradiated food
Report of a Joint FAO/IAEA/WHO Expert Committee (34 pages) .......... 3.—

No. 660 (1981) Nongonococcal urethritis and other selected sexually transmitted diseases of public health importance
Report of a WHO Scientific Group (142 pages) ............................. 9.—

No. 661 (1981) Rapid laboratory techniques for the diagnosis of viral infections
Report of a WHO Scientific Group (60 pages) ............................. 4.—

No. 662 (1981) Health effects of combined exposures in the work environment
Report of a WHO Expert Committee (76 pages) ............................. 5.—

No. 663 (1981) Education and training in occupational health, safety and ergonomics
Eighth report of the Joint ILO/WHO Committee on Occupational Health (48 pages) ................................................. 3.—

No. 664 (1981) Recommended health-based limits in occupational exposure to selected organic solvents
Report of a WHO Study Group (84 pages) ..................................... 6.—

Report of a WHO Study Group (88 pages) ..................................... 6.—

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Report of a WHO Scientific Group (152 pages) ............................. 10.—

No. 667 (1981) The role of the health sector in food and nutrition
Report of a WHO Expert Committee (92 pages) ............................. 6.—

No. 668 (1981) Disability prevention and rehabilitation
Report of a WHO Expert Committee (40 pages) ............................. 3.—

Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives (48 pages) ................................................. 3.—

Report of a WHO Scientific Group (120 pages) ............................. 8.—

No. 671 (1982) Tuberculosis control
Report of a Joint IUAT/WHO Study Group (26 pages) ........................ 3.—