Update
Le point

Articles in the **Update** *series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, covering many different aspects of the biomedical sciences and public health. Most of the articles are written by acknowledged experts on the subject.*

Les articles de la rubrique **Le point** *fournissent un bilan concis et fiable de la situation actuelle dans les domaines considérés, couvrant de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés par les spécialistes les plus autorisés.*

Bulletin of the World Health Organization, **65** (6): 769–777 (1987)

Streptococcal diseases worldwide: present status and prospects*

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Infections caused by streptococci pathogenic for man are some of the most common bacterial diseases in temperate zones and occur very frequently in tropical and subtropical countries. The highest morbidity occurs from infections caused by group A streptococci; these infections can lead to rheumatic fever and acute glomerulonephritis. The incidence of rheumatic fever and the prevalence of rheumatic heart disease are several times higher in tropical countries than temperate countries.

Recent developments in fundamental and applied research are throwing light on various aspects of the problem, e.g., the rapid (non-culture) identification of group A streptococcal infection. Analyses of the chemical structure of the M-protein molecule of group A streptococcus and of the biological properties of the epitopes of the M-protein have provided encouraging results. Furthermore, synthetic analogues of the protective immunodominant polypeptides of the M-protein have been prepared. The prospect of a streptococcal vaccine for preventing group A streptococcal diseases is thus more realistic.

The control of infections caused by group B streptococci is important for the health of neonates. The identification of the chemical structure of the major group B streptococcal types may lead to development of a vaccine in the future. An alternative approach would entail the use of anti-group-B immunoglobulins, but a number of questions have to be answered before the new control measures can be introduced. The streptococci causing bacterial pneumonia, subacute bacterial endocarditis and possibly dental caries have been widely studied and promising advances have been made towards the introduction of better control of the diseases caused by these pathogens.

CLINICAL AND PUBLIC HEALTH ASPECTS

The first century after the discovery of the bacterium causing streptococcal infections was marked during the 1970s. Streptococci constitute a large number of species with

* A French translation of this article will appear in a later issue of the *Bulletin*.

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diverse biological properties, and they produce various clinical symptoms. At the present time, much information is available on the streptococcus and the host, and on various features of interaction between the two, so that control measures can be introduced against these infections in situations requiring intervention (*1*, *2*). However, despite improvements in diagnosis, therapy and prevention, the control of infections caused by pathogenic streptococci is far from satisfactory. Several important questions remain unanswered, and their clarification is a prerequisite to further advances in diagnostic procedures and control measures.

Clinical manifestations

Diverse pathogenic mechanisms are involved in streptococcal infections resulting in a variety of clinical manifestations. The clinical pattern varies depending on the particular species of streptococcus involved, the site of initial colonization, the tissue or organ affected, and the status of the host.

Haemolytic streptococci, in particular those of group A (*Streptococcus pyogenes*), are by far the most frequent streptococcal pathogens in man. Group A organisms produce disease with extremely varied symptomatology, primary infections often presenting with tonsillitis, pharyngitis and scarlet fever, but sometimes tracheitis, laryngitis, tracheobronchitis, bronchitis, pneumonia, erysipelas and cellulitis. Septic complications include cervical lymphadenitis, otitis media, sinusitis, mastoiditis, meningitis, empyema, peritonitis and endocarditis. These group A infections may lead to rheumatic fever and acute glomerulonephritis.

Infections in newborns and urogenital tract infections in women are the most serious forms of disease produced by group B streptococci.

Group D organisms are very common in humans. They are normally found in the gastrointestinal and genito-urinary tracts, and on the skin. Under specific conditions, group D streptococci cause subacute or acute systemic infections, or localized septic processes. It is known that they most commonly cause urinary tract infections and also infective endocarditis.

Groups C, G and F streptococci frequently colonize the pharynx and sporadically produce upper respiratory tract disease, and they can provoke localized sepsis at other sites.

The alpha-haemolytic (*S. viridans*) or non-haemolytic streptococci, not groupable within Lancefield's classification, are frequently encountered in the upper respiratory tract in man and sometimes in other body sites. These streptococci are frequently the cause of postoperative purulent complications occurring as nosocomial endogenous or exogenous infections, and are the most common cause of infective endocarditis.

Streptococci are thought to be associated with dental caries but this suggestion requires further study. The hypothesis concerns the possible cariogenicity of *S. mutans* and *S. sanguis*.

Anaerobic streptococci cause suppurative inflammatory processes under anaerobic conditions in the presence of other anaerobic microbes.

S. pneumoniae and the clinical patterns produced by this organism have their own particular features but these are not reviewed in this article.

Epidemiology

Studies of the occurrence and spread of infections caused by streptococci pathogenic for man have clarified major epidemiological characteristics of these illnesses.

Group A streptococci are transmitted from person to person through the air when there is close contact between individuals. The organisms are mainly conveyed by relatively large droplets up to a distance of about three metres. Symptoms of respiratory disease

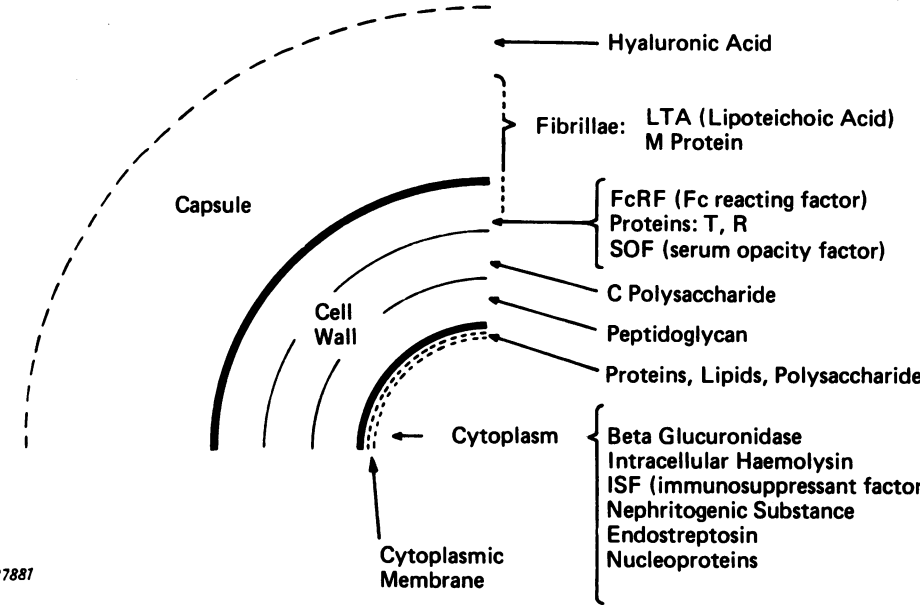

Fig. 1. Schematic drawing of the components of the capsule and wall of group A streptococcus.

usually develop within two to three days. Acquisition rates are highest upon exposure to acute infection and decrease considerably as the carrier state progresses. Patients harbouring streptococci in the nose are particularly likely to transmit infection. The organism can also be dispersed in the air and on the surface of fomites by carriers, but as a rule these streptococci are not a source of respiratory infection.

In order to cause disease, a microorganism must have certain biological characteristics, the most essential being its ability to adhere to epithelial cells (by means of lipoteichoic acid located on the fibrillae covering the cell wall) and its virulence (presence of the type-specific M-protein, which protects the streptococci from phagocytosis) (Fig. 1). The host's susceptibility is obviously determined by a number of factors, the best known and most important of which is the lack of type-specific immunity.

Human reservoirs are the only major source of microorganisms in respiratory streptococcal infection. The density and magnitude of close contact or overcrowding is the decisive environmental factor in the spread of infection while climate and socioeconomic status play an indirect role only.

The epidemiology of rheumatic fever and acute glomerulonephritis displays all the major characteristics of the epidemiology of acute streptococcal infection. The latent period preceding a rheumatic fever attack is usually two or three weeks, but it can vary from 5 to 45 days. In acute glomerulonephritis the latent period may vary from one to four weeks.

Unlike the group A infections, which can occur either sporadically or in epidemics, the infections caused by other streptococci are almost always sporadic owing to their different epidemiological characteristics. Exceptions to this rule are the foodborne tonsillo-

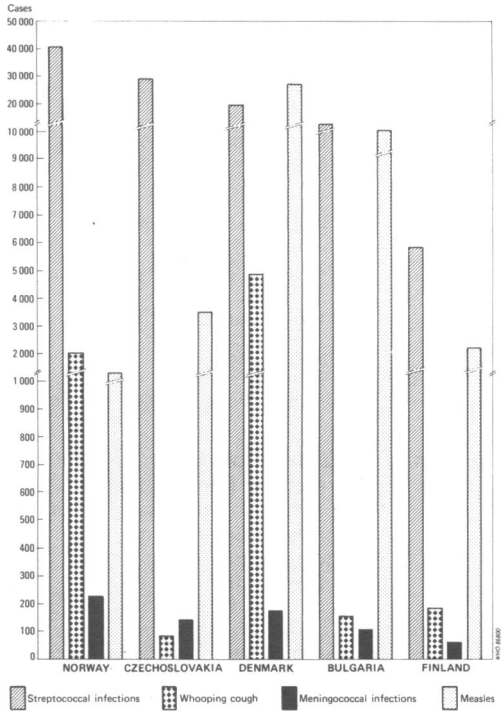

Fig. 2. Incidence of streptococcal infections (sore throat and scarlet fever), whooping cough, meningococcal infections and measles reported in 1980 in five European countries.

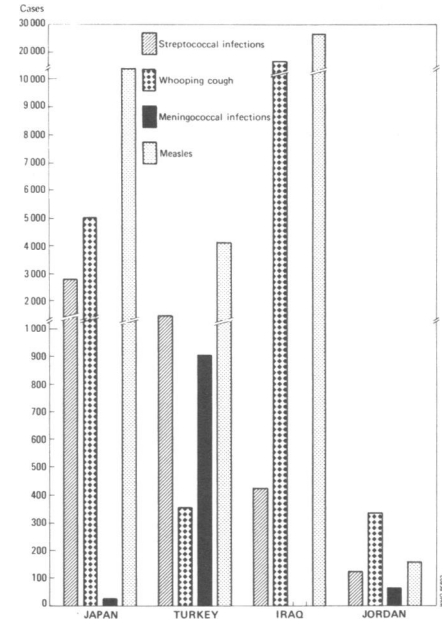

Fig. 3. Incidence of streptococcal infections (sore throat and scarlet fever), whooping cough, meningococcal infections and measles reported in 1980 in four Asian countries.

pharyngitis outbreaks caused by groups G and C streptococci, and group B neonatal hospital infections.

Data on the carriers of beta-haemolytic streptococci, on the incidence of streptococcal infections, rheumatic fever and acute glomerulonephritis, and on the prevalence of rheumatic heart disease have served to document the health and economic impact of the streptococcal diseases complex in various parts of the world.

Prospective studies have disclosed that in temperate climates 20% or more of individuals may be harbouring haemolytic streptococci in some situations. Data reported in recent years from tropical and subtropical countries indicate that the carrier state is often no less in these areas. The incidence of streptococcal acute upper respiratory tract disease in temperate zones is 5–15 cases per 100 individuals per year.

Statistical data obtained from some European countries demonstrate fairly widespread manifestations of streptococcal infections such as sore throat and scarlet fever (*17*) (Fig. 2). Moreover, there is sometimes a much higher incidence of these diseases than there is of other respiratory infections such as whooping cough, meningitis and measles. In Czechoslovakia, for example, 29 213 cases of streptococcal upper respiratory tract infections (sore throat and scarlet fever) were registered in 1980, compared with 84 cases

of whooping cough, 142 cases of meningitis and 3533 cases of measles. In Norway, 40 230 cases of streptococcal infections were reported, the total number of cases of all the other above-mentioned diseases amounting to 3439. Corresponding data for Finland are 5867 and 2398 cases, respectively.

Fig. 3 demonstrates comparative data on cases of streptococcal upper respiratory tract infection (sore throat and scarlet fever), as well as cases of whooping cough, meningococcal meningitis and measles reported from some Asian countries.

It is understood that the completeness of the data, particularly in the case of streptococcal infections, largely depends on the reporting system employed, the clinical and/or laboratory criteria used, etc. These data alone, therefore, cannot adequately reflect the incidence of streptococcal infection. Nevertheless, the figures provide us with a general picture of these communicable diseases.

Schoolchildren run the highest risk of contracting group A streptococcal infection and the incidence rates can also be relatively high in closed or semi-closed communities, such as military camps.

It is well known that streptococcal diseases may occur both in sporadic and epidemic forms. Explosive outbreaks of streptococcal sore throat may result not only from airborne transmission in communities but also from contaminated food (*3, 4*).

Group A streptococci

Group A streptococcus is highly pathogenic in wounds caused by burns; forty years ago it appeared in over 75% of patients admitted with burns, infection with *S. pyogenes* being a serious and almost inevitable complication of burns until the 1940s. Since then, there has been a dramatic reduction in such infections as a result of the introduction of aseptic methods for management of patients and the use of antimicrobial prophylaxis. Although *S. pyogenes* can now be controlled, the streptococcal infection due to it in burns may still occur. Thus, according to recent data from the Birmingham Accident Hospital (*5*), *S. pyogenes* was isolated from burn wound swabs in 3.7% of cases. Another outbreak caused by a virulent M-type 49 group A streptococcus made it possible to document the invasiveness of this pathogen in burned victims (*6*).

In hot climates the carrier state of haemolytic streptococci is quite common[a] and tends to produce rather mild respiratory disorders, the frequency of which has not yet been adequately estimated. However, skin infections due to haemolytic streptococci are very common in such areas, and their prevalence can even reach 20% or more of the child population in hot and humid seasons. Epidemiological studies on the prevalence of pyoderma among Amerindian populations of Amazonia in Brazil are one example (*7*). When the attack rates for the entire population sample were calculated by 5-year age intervals, the highest rate was found to occur among the under-5-year-olds (31%), and the highest prevalence rate (38%) occurred among the 3-year-old group. Every pathogen-positive culture of the pyoderma lesions contained *S. pyogenes*, which was the only pathogen recovered in cultures from 44% of the 39 individuals tested.

The incidence of rheumatic fever as the sequela of group A streptococcal infection has declined in the developed countries. In the USA and European countries the incidence is mostly some two attacks per 100 000 population per year. Morbidity from rheumatic heart disease has also declined markedly, although not to the same extent. Sporadic reports, however, indicate that rheumatic fever has not disappeared and its eradication cannot be expected as long as group A streptococci circulate in the population. The recent outbreaks

[a] ROTTA, J. & FACKLAM, R. R. *Manual of microbiological methods of streptococcal infections and their sequelae.* Unpublished document, WHO/BAC/80.1, 1980.

of rheumatic fever in the USA confirm the continuing risk (*8*).

Over the last two or three decades, data on the magnitude of the problem in an increasing number of countries with hot climates show that rheumatic fever occurs frequently and rheumatic heart disease is the commonest form of heart disease. In India, for example, the prevalence of rheumatic heart disease in children has been estimated at between 2 and 10 per 1000. As 43% of the population are under 14 years old, some three million children could be suffering from rheumatic heart disease in this country. The resulting costs are high not only in terms of suffering, but also in terms of enormous loss of productive human resources and the need for heavy expenditures to care for the millions of patients thus afflicted. The results of a study (*9*) carried out at the University College Hospital, Ibadan, Nigeria, showed that the cost of medical treatment of chronic rheumatic heart disease and other economic implications of the disease accounted for 4.4% of the average income per family. In addition to payments due to medical expenses (drugs, hospitalization, etc.), other economic losses are difficult or impossible to assess. Even when the disease is not immediately fatal, the infected children remain chronic invalids who pose a serious problem to the nation in terms of loss of manpower.

In general, the prevalence of rheumatic heart disease in schoolchildren is about 0.1 per 1000 in developed countries and much higher (1–22 per 1000) in developing countries. These figures indicate that there may be about 1.5 million children in industrialized countries and 30 million children in developing countries with rheumatic heart disease who are in need of care.

Group B and other streptococci

Group B streptococci colonize 10–30% of all women and are responsible for one of the most serious bacterial infections in neonates. Studies in the USA and other countries have shown that 10–20% of all newborn infants are colonized by group B streptococci (*10*). Only a small number of these colonized infants, however, develop symptomatic group B streptococcal disease (respiratory distress, sepsis, meningitis). Current clinical and laboratory procedures unfortunately do not provide rapid and selective identification of these high-risk infants or their mothers. For this reason the mortality rates due to neonatal group B streptococcal diseases are around 50% — among the highest rates of any bacterial disease in newborn infants.

Infections caused by streptococci other than group A and B may be sporadic or may occur in a high frequency in a given area at a particular period of time. No generally valid figures on the carrier state and morbidity can be drawn from the information collected so far. There are also considerable variations in the incidence and prevalence of these infections.

DIAGNOSIS AND CONTROL

The *diagnosis* of streptococcal infections based on clinical symptoms alone is highly unreliable, especially in the case of upper respiratory infections. Microbiological confirmation of the clinical diagnosis is, therefore, essential. However, microbiological examination of tonsillopharyngitis cases in outpatient clinics, using current laboratory techniques, requires at least one or two days. The methods, based on procedures that were introduced several decades ago, entail sampling of the material, cultivation on blood-agar plates overnight, identification of streptococcal colonies, and determination of the serological group.

The new rapid, direct (non-culture) techniques for the identification of group A

streptococci in clinical specimens represent a real breakthrough in microbiological diagnosis. One of these techniques is the co-agglutination method, the results of which are available in five minutes after the specimen has been taken. There is no need for laboratory equipment and the technique can be performed by untrained personnel. The reliability and reproducibility of this method has been confirmed in an international collaborative study, coordinated by WHO (*18*). Use of this method will prevent the unnecessary administration of penicillin, with considerable health and economic benefits.

Indirect diagnosis of streptococcal infections by antibody measurements is almost entirely restricted to disease caused by group A streptococci. Titration of antistreptolysin O (ASO) and antideoxyribonuclease B (ADN-B), which is the most commonly used method, is recommended in current practice, particularly for cases of rheumatic fever and acute glomerulonephritis. The so-called streptozyme test, although simple and widely used in some countries, still requires further improvement to confirm its value. There are a number of other serological tests, such as the antistreptokinase, antidiphosphopyridin-dinucleotidase, antihyaluronidase, and antipolysaccharide antibody test, but these are employed considerably less frequently than ASO and ADN-B.

The typing of group A streptococci according to the M, OF and T antigens and group B streptococci according to the capsular polysaccharides is important, both for epidemiological reasons and for the future development of streptococcal vaccines. Infections caused by streptococci other than group A must be examined by conventional laboratory culture methods, and isolated strains have to be classified into the particular species of the genus *Streptococcus*.

The *control* of streptococcal infections is dependent on rapid diagnosis and early therapy using antibiotics or on effective countermeasures for prevention. In group A streptococcal infections, penicillin is the drug of choice for therapy. Early treatment of an acute infection is primary prevention against the sequelae of that infection, especially rheumatic fever and rheumatic heart disease, and should be the main goal of streptococcal disease control.

Preventive measures now available or for future consideration against group A infections can be divided into three categories:

—general preventive measures (e.g., prevention of overcrowding, when necessary for epidemiological reasons);
—prophylaxis by antibiotics and sulfonamides;
—specific immunization and enhancement of non-specific resistance (e.g., the prospect of an effective and safe M-protein vaccine or the induction of non-specific resistance).

With regard to preventive measures by antibiotics, the best means available at present is the administration of penicillin. This approach has been shown to be highly effective in epidemic or risk situations in military camps, schools and other closed or semi-closed communities.

Long-term penicillin prophylaxis (1.2 ml or 1.2 million units of benzathine penicillin in adults and 0.6 ml or 600 000 units in children) at three-week intervals should be administered to all individuals who have experienced an attack of rheumatic fever or are suffering from rheumatic heart disease (secondary prevention).

For a number of reasons, however, this form of control is not considered to be the final solution to the problem. The application of penicillin over a long period of time may have deleterious effects in some individuals. It is not known at present how the circulation of group A streptococci among the population can be suppressed; as it is anticipated that these infections will present a health problem for several decades to come, there is a strong case for the study of new approaches to prevent group A streptococcal infections.

Much attention is now being paid to the development of a streptococcal group A vaccine,

and studies have already been performed on its preparation, safety and efficacy. It is known that, among the group A streptococci, the microorganism is protected from phagocytosis by the M-protein which is type-specific; over 70 M-protein types are known. Antibody to M-protein neutralizes its antiphagocytic effect and provides immunity, which in group A infections is type-specific. The vaccines used in volunteers have so far been effective, but there is some concern about their side-effects. For example, the presence of polypeptide(s) cross-reactive with the sarcolemmal membrane of heart tissue in some M-protein preparations must be avoided (*11*). Techniques have now been developed for the elimination or separation of these undesirable elements by means of brief pepsin digestion and further purification.

A major contribution was recently made on the molecular level of M-protein research. This was the identification in the type 24 M-protein molecule of repeating covalent polypeptide structures, each of which carries the immunodeterminant type-specific and protective group (*12*). The extensive sequence repeats, however, are absent in type 5 M-protein (*13*). The determinants on the M-protein molecule may bear some degree of heterogeneity, and the antibody to some polypeptides of the M-protein molecule can also opsonize a heterologous type (or types) (*14*).

The identification of amino-acid sequences in M-protein molecules prompted the synthesis of peptides analogous to polypeptide subunits of the native molecule. A recently reported successful transfer of genetic information on M-protein production from M-6 streptococcus to *E. coli* and the production of M-6 protein by this *E. coli* hybrid represents another approach in the streptococcal vaccine project. These advances in fundamental research have provided important information which will help the development of a useful vaccine in the future. It is now clearly understood that the vaccine should be polyvalent, that the M-protein or its immunodeterminant structures (whether native or synthetic) should be deprived of components producing side-effects, and that the antibody response should be sufficiently strong and long-lasting. Persons with rheumatic fever or rheumatic heart disease and others at high risk of contracting streptococcal diseases are suitable candidates for vaccination.

Current approaches to control group B streptococcal infections are not satisfactory, particularly in the case of life-threatening infections of newborns. There is a need for new techniques to prevent the transfer of the organism from mother to child. The hygienic and antiseptic measures taken and the administration of antibiotics before delivery have proved to be insufficiently effective. This situation provided the stimulus for research on a group B streptococcal vaccine composed of purified capsular polysaccharides (for active immunization) and on the use of hyperimmune serum with anti-group-B type immunoglobulins (for passive protection). Technology has been developed for the isolation and purification of capsular type-specific polysaccharides of group B streptococci, the chemical structure of the antigens has been defined, and their immunogenicity determined (*15*). Both approaches have their advocates as well as opponents. Several questions remain unanswered, such as whom to vaccinate when the vaccine is made available, when to vaccinate mothers, etc. Although the data available are quite encouraging, more information is required before the vaccine can be employed in practice.

Current control measures for infections caused by streptococci other than group A and B are based on general preventive techniques and antibiotic prophylaxis alone. No new approaches are planned for the near future, with the possible exception of the control of dental caries by a vaccine if *S. mutans* is proved to have an etiopathogenic relationship with this disease in man and if the protective antigens are conclusively identified (*16*).

Since the problem of diseases due to the streptococcal complex will apparently continue for the next few decades, basic and applied research as well as public health activities focused on primary health services should be further developed. The circulation of streptococci causing infection in man cannot be effectively suppressed by the measures used at

present. These infections are of considerable health and economic importance for the population in all parts of the world and merit further attention.

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