74 Rheumatic Fever

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Rheumatic fever is the leading cause of acquired heart disease in children and young adults worldwide. Initiated by a pharyngeal infection with group A beta-hemolytic streptococci (GAS) and following a latent period of approximately 2 to 3 weeks, the illness is characterized by acute inflammation of the heart, joints, skin, subcutaneous tissue, and central nervous system. Pathologically, the inflammatory process causes damage to collagen fibrils and connective tissue ground substance (i.e., fibrinoid degeneration), and thus rheumatic fever is classified as a connective tissue or collagen vascular disease.

The destructive effect on the heart valves leads to the chronic sequelae of the disease—rheumatic heart disease (RHD)—with serious hemodynamic disturbances causing cardiac failure, and other complications such as stoke and infective endocarditis. Referring to the fleeting arthritis and damaging carditis characteristic of rheumatic fever, the French physician Ernst-Charles Lasègue famously said in 1884, "Pathologists have long known that rheumatic fever licks at the joints, but bites at the heart." Almost all cases of rheumatic fever and RHD and associated deaths are entirely preventable.

EPIDEMIOLOGY

The burden of rheumatic fever and RHD has been characterized by at least four changing patterns over the past 150 years (**Fig. 74.1**). The first pattern represents the preantibiotic fall in incidence of rheumatic fever that is typical of industrialized countries (curve A, **Fig. 74.1**). For example, in the United States the incidence per 100,000 population was 100 at the start of 20th century, 45 to 65 between 1935 and 1960, and is currently estimated to be less than 10 cases per 100,000.[1] The decrease in rheumatic fever incidence preceded the introduction of antibiotics in the 1940s and is almost certainly the result of improved socioeconomic standards, less overcrowded housing, and improved access to medical care.

The second pattern is characterized by a persistently high incidence of rheumatic fever in developing regions and among indigenous populations of some developed countries, such as Australia and New Zealand (curve B, **Fig. 74.1**). The incidence of rheumatic fever among 5-to 14-year-old indigenous Australian children is as high as 162 per 100,000 per year in males, and 228 per 100,000 per year in females.[2] This hyperendemic pattern of rheumatic fever affects the majority of the population of the world who live in Africa, Middle East, Asia, eastern Europe, South America, and indigenous communities of Australasia.[3]

Third, some developing countries, such as Cuba, Costa Rica, the French Islands of Martinique and Guadeloupe, and Tunisia, have experienced a falling incidence of rheumatic fever following the implementation of comprehensive public health programs of primary and secondary prevention of rheumatic fever[4] (curve C, **Fig. 74.1**). By contrast, African countries that have not implemented public health programs for prevention of rheumatic fever continue to experience a high incidence of rheumatic fever and RHD.[5]

Outbreaks of rheumatic fever have been reported in affluent communities of the United States and Italy[6] (see Classic References, Veasy). The epidemiologic transition in the former Soviet Union has been associated not only with an increase in mortality rates from atherosclerotic diseases and trauma in Russia, but also in a sustained resurgence of rheumatic fever and RHD in central Asia.[7] The incidence of rheumatic fever fell in central Asia to the same levels as Japan in the middle 1970s, but rose sharply in the post-Soviet period to levels associated with developing countries (curve D, **Fig. 74.1**). Among developing countries, Kyrgyzstan probably has the highest incidence of rheumatic fever and RHD, approximately 543 per 100,000 population per year, thus earning the central Asian republics the dubious distinction of being the rheumatic fever "hot spot" of the world. The resurgence of rheumatic fever in the formerly Soviet republics may reflect the weakening of the primary health care system and the economic crisis of the post-Soviet period (see Classic References, Tulchinsky and Varavikova).

PATHOGENESIS

Rheumatic fever is a multifactorial disease that follows GAS pharyngitis (the agent) in a susceptible individual (the host) who lives under deprived social conditions (the environment). The theory of *molecular mimicry* holds that GAS pharyngitis triggers an autoimmune response to epitopes in the organism that cross-react with similar epitopes in the heart, brain, joints and skin, and repeated episodes of rheumatic fever lead to RHD[1,8] (**Fig. 74.2**).

The Agent

Epidemiologic and immunologic observations together with the preventive effect of antibiotic treatment for pharyngitis demonstrated in clinical trials strongly support the causative role of untreated GAS pharyngitis in rheumatic fever.[9] Streptococcal skin infection is believed not to cause rheumatic fever. However, a report of rheumatic fever following streptococcal wound infection (see Classic References, Popat and Riding), as well as the high prevalence of pyoderma with relative paucity of streptococcal pharyngitis in aboriginal communities of Australasia with a high incidence of rheumatic fever, raised questions about the link between streptococcal skin infection and rheumatic fever.[10] Although effective antibiotic treatment substantially reduces the risk of rheumatic fever, in situations of untreated epidemic GAS pharyngitis, up to 3% of patients develop the disease.[11]

The hypothesis of molecular mimicry in the pathogenesis of rheumatic fever has been reviewed.[1,9] There is evidence that patients with RHD have cross-reactive autoantibodies that target the dominant GAS epitope of the group A carbohydrate, *N*-acetyl-beta-D-glucosamine (GlcNAc), and laminin and laminar basement membrane in heart valve endothelium. T cells in peripheral blood and heart valves of patients with RHD

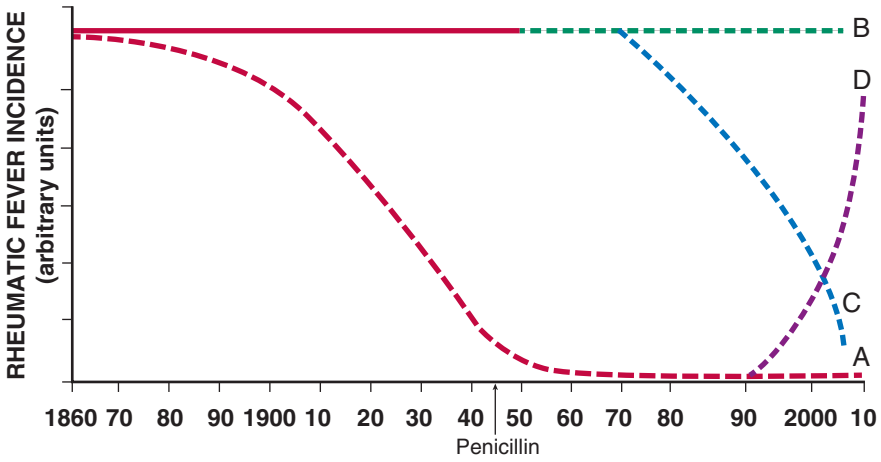

FIGURE 74.1 Incidence of rheumatic fever: four patterns over the past 150 years. Curve A represents the preantibiotic fall in the incidence of rheumatic fever that is typical of industrialized countries. Curve B is typical of the persistent high incidence of rheumatic fever in regions of the world with no comprehensive program for prevention, such as Africa and south Asia. Curve C shows the postantibiotic fall in the incidence of rheumatic fever in countries that instituted comprehensive programs for primary and secondary prevention of rheumatic fever, such as Cuba, Costa Rica, Martinique, and Guadeloupe. Curve D shows the fall and rise in the incidence of rheumatic fever in the formerly Soviet republics of central Asia. (Modified from Parry E, Godfrey R, Mabey D, Gill G, editors. Principles of Medicine in Africa. 3rd ed. Cambridge: Cambridge University Press; 2004, p 861.)

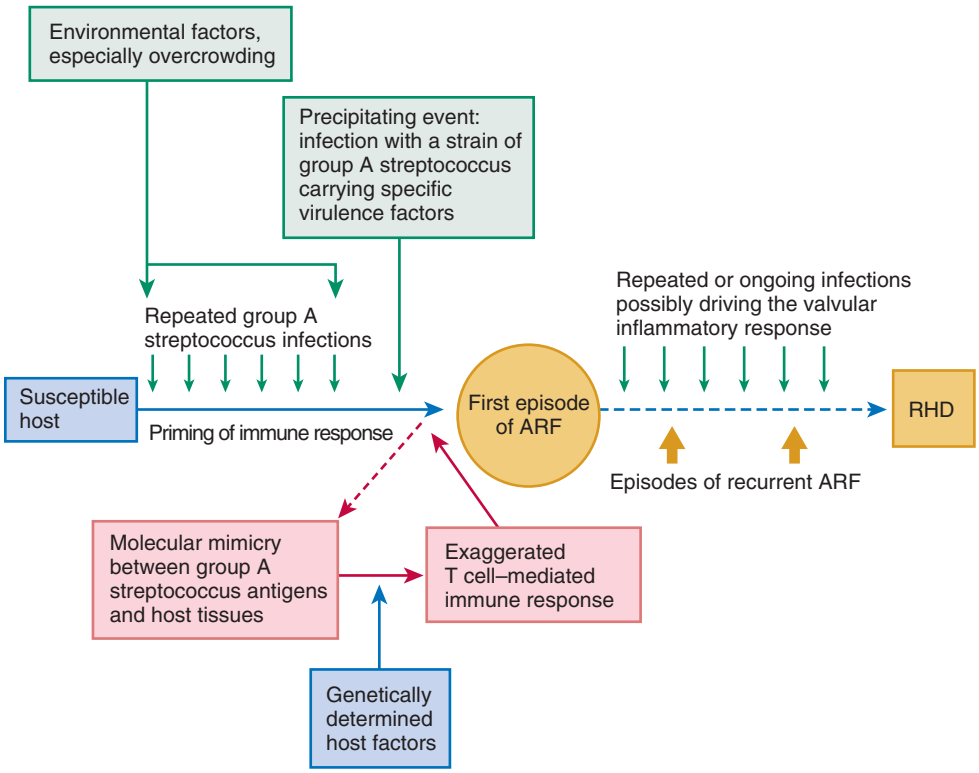

FIGURE 74.2 Pathogenesis of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). (From Carapetis J, McDonald M, Wilson NJ. Acute rheumatic fever. Lancet 2005;366:155.)

cross-react with streptococcal M protein and cardiac myosin. Furthermore, autoantibodies against the GAS carbohydrate epitope GlcNAc and cardiac myosin appear during progression of RHD. In addition, autoantibodies against collagen that are not cross-reactive may form because of the release of collagen from damaged valves.

The *two-hit hypothesis* for the initiation of disease proposes that antibody attack of valve endothelium facilitates the extravasation of T cells through activated epithelium into valve tissue, leading to the formation of granulomatous nodules called Aschoff bodies that are characteristic of rheumatic myocarditis. The area of central necrosis is surrounded by a ring of plump histiocytes called Anitschkow cells (**Fig. 74.3**). These nodules were discovered independently by Ludwig Aschoff and Paul Rudolf Geipel and thus are occasionally called Aschoff-Geipel bodies.

In *Sydenham chorea,* human monoclonal antibodies (mAbs) derived from patients with disease target GlcNAc, gangliosides, and dopamine receptors are found on the surface of neuronal cells in the brain. Human mAbs and autoantibodies in Sydenham chorea activate calcium/calmodulin-dependent protein kinase II (CaMKII) in neuronal cells and recognize the intracellular protein biomarker tubulin. Therefore the theme of molecular mimicry in rheumatic fever is characterized by the recognition of targeted intracellular biomarker antigens (cardiac myosin and brain tubulin), while targeting extracellular membrane antigens (laminin on valve surface endothelium or lysoganglioside and dopamine receptors in the brain).[1,9]

The Host

Several lines of epidemiologic evidence support the role of hereditary factors in susceptibility to rheumatic fever. First, the lifetime cumulative incidence of rheumatic fever in populations exposed to rheumatogenic GAS infection is constant at 3% to 6% regardless of geography or ethnicity.[12] This suggests that the proportion of susceptible individuals is the same in all continental populations of the world.[13]

Second, the familial aggregation of rheumatic fever was reported by Cheadle as far back as 1889.[13] Cheadle reported that the chance of an individual with a family history of rheumatic fever acquiring the disease is "nearly 5 times as great as that of an individual who has no such hereditary taint." The familial aggregation of RHD has been supported by a study of children raised separately from parents with RHD, who had a relative risk of 2.93 for the development of rheumatic fever compared with children whose parents did not have RHD.[13] Also, a study of 435 twin pairs found that the risk of rheumatic fever in a monozygotic twin when the co-twin previously had rheumatic fever is more than six times greater than that in dizygotic twins. The heritability of rheumatic fever is 60%, which highlights the importance of heredity as a major susceptibility factor of the disease.[14]

Numerous studies have been conducted to search for specific genetic susceptibility factors in rheumatic fever.[15] Several genes controlling the adaptive immune response (e.g., HLA class II alleles, cytotoxic T cell lymphocyte antigen 4), the innate immune response (e.g., ficolin 2, mannose-binding lectin 2, receptor for Fc fragments of IgG, Toll-like receptor 2), cytokine genes (e.g., tumor necrosis factor alpha, transforming growth factor beta, interleukin-1 receptor A, interleukin-10), and B cell alloantigens have been implicated in the development of the disease. Although significant associations have been found between genetic factors and rheumatic fever, study results either conflict with each other or are not replicated.[13] Therefore, it is not possible at present to predict the individuals who are at risk of developing rheumatic fever following an episode of untreated streptococcal pharyngitis.

The Environment

It is well known that rheumatic fever is generally associated with low socioeconomic status. The incidence of rheumatic fever has been falling consistently in industrialized countries since the mid-19th century, independently of the advent of penicillin, possibly because of less crowding, improved housing and nutritional conditions, higher levels

of parental employment, and better access to health care (curve A, **Fig. 74.1**). In New Zealand, the risk of rheumatic fever is linked to high levels of deprivation based on household income, access to telephone and car, education level, and housing.[16] The impact of the social gradient has also been illustrated in Uganda, where an increased risk of RHD is associated with overcrowding and unemployment. Furthermore, there was interaction between overcrowding and distance from the nearest health center, suggesting that the effect of overcrowding on the risk of acquiring RHD increases with every kilometer increase from the nearest health center.[17] In addition, schoolchildren of lower socioeconomic status have a higher prevalence of disease and more advanced disease in an echocardiographic screening study of RHD in Uganda.[18]

CLINICAL FEATURES

The typical attack of rheumatic fever follows an episode of streptococcal pharyngitis after a latent period of 2 to 3 weeks. During the latent period there is no clinical or laboratory evidence of active inflammation. However, as many as one third of patients who develop rheumatic fever do so after asymptomatic GAS, and in outbreaks, up 58% of patients have no symptoms of pharyngitis. This is one of the potential barriers to the effectiveness of primary prevention of rheumatic fever solely with antibiotic treatment of GAS pharyngitis and provides the justification for the development of an anti-GAS vaccine as one of the strategies for the control of rheumatic fever and other streptococcal diseases.

Rheumatic fever occurs most frequently in children between ages 4 and 15 years. In developing countries such as Saudi Arabia and India, juvenile mitral stenosis may occur at age 3 to 5 years.[19] The prevalence of the various clinical features varies in different studies depending on whether the patients are studied prospectively or in retrospect. The illness usually begins with a high fever, but in some patients the fever may be low grade or absent. The most common of the major criteria is *polyarthritis*, which occurs in two thirds to three quarters of the patients, followed by carditis and chorea.

Arthritis

Joint involvement is more common (almost 100%), and more severe in young adults than in teenagers (82%) and children (66%).[20] The joint pain is typically described as "migratory," which refers to the sequential involvement of joints, with inflammation resolving in one joint and then beginning in another joint. In some cases the joint involvement may be additive rather than migratory, with simultaneous involvement of several joints. In untreated patients the number of joints involved may vary from 6 to 16.[20]

The affected joint may be inflamed for only a few days to 1 week before the inflammation subsides. The polyarthritis is severe for approximately 1 week in two thirds of patients and may last another 1 to 2 weeks in the remainder before it resolves completely. If joint swelling persists after 4 weeks, it becomes necessary to consider other conditions, such as juvenile idiopathic arthritis or systemic lupus erythematosus (SLE).[20]

At the onset of the illness the joint involvement is asymmetric and usually affects the lower limbs initially before spreading to the upper limbs. Monoarthritis has been reported in 17% to 25% of patients.[21] The large joints such as the knees, ankles, elbows, and wrists are most frequently involved. The hip, shoulder, and small joints of the hands and feet are less frequently involved. Analysis of the synovial fluid has shown the presence of sterile inflammatory fluid. There may be a reduction in complement components C1q, C3, and C4, suggesting their consumption by immune complexes. Radiographs may show features of a joint effusion, but no other abnormalities are noted.[20]

Jaccoud arthritis or arthropathy (or chronic post–rheumatic fever arthropathy) is a rare manifestation of rheumatic fever characterized by deformities of the fingers and toes (**Fig. 74.4**). The condition may occur after repeated attacks of rheumatic fever and results from recurrent inflammation of the fibrous articular capsule. There is ulnar deviation of the fingers, especially the fourth and fifth fingers, flexion of the metacarpophalangeal joints, and hyperextension of the proximal interphalangeal joints (i.e., swan neck deformity). The hand is usually painless, and there are no signs of inflammation. The deformities are usually correctible but may become fixed in the later stages. There are no true erosions on radiography, and the rheumatoid factor is usually negative. A similar form of arthropathy is seen in patients with SLE.[20]

The arthritis of rheumatic fever responds promptly to nonsteroidal anti-inflammatory drugs, and thus the classic presentation of a migratory polyarthritis may be infrequent where self-medication with NSAIDs, or their prescription without considering the diagnosis, is common. The apparent fall in incidence of rheumatic fever in some developing countries may be related to indiscriminate use of NSAIDs without considering a diagnosis of rheumatic fever.[22] The differential diagnosis

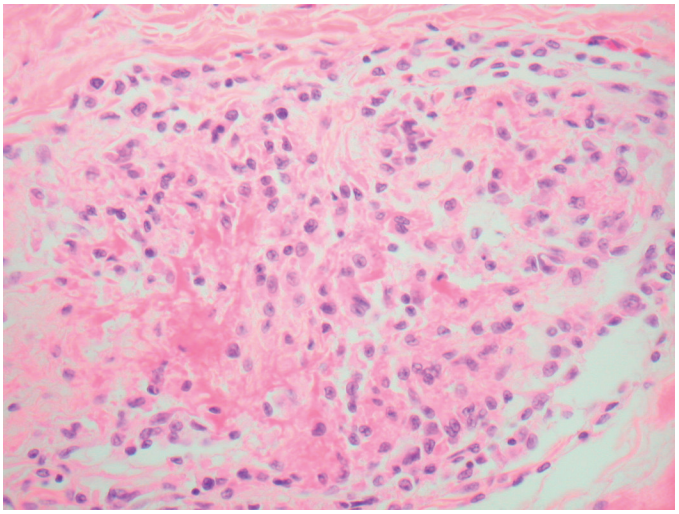

FIGURE 74.3 The Aschoff body of rheumatic fever. Photomicrograph of an Aschoff nodule from the heart in a case of acute rheumatic fever. The nodule is composed of Anitschkow cells; these have clear nuclei with a central bar of chromatin, said to resemble a caterpillar. There is a central area of fibrin. This central necrosis is further surrounded by a mononuclear cell infiltrate. Myocardial fibers adjacent to the Aschoff body are undergoing destruction. (From Sebire NJ, Ashworth M, Malone M, Jacques TS, editors. Diagnostic Pediatric Surgical Pathology. London: Churchill Livingstone; 2010.)

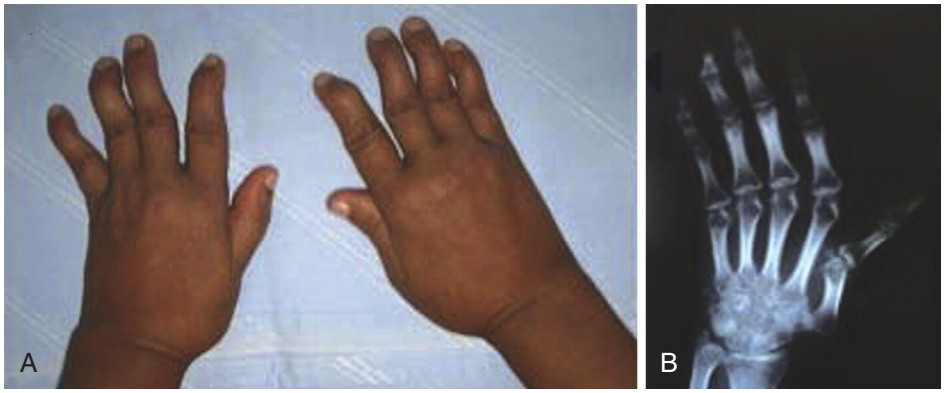

FIGURE 74.4 Post–rheumatic fever Jaccoud arthropathy. **A,** Swan neck deformity in Jaccoud arthropathy, with ulnar deviation and metacarpophalangeal subluxation. **B,** Plain radiograph of left hand showing deformities but not erosions. (From Santiago MB: Jaccoud's arthropathy. Best Prac Res Clin Rheumatol 2011;25:715.)

of polyarticular arthritis in children and adolescents includes poststreptococcal reactive arthritis, other autoimmune diseases, septic arthritis, infective endocarditis, Lyme disease, lymphoma/leukemia, viral arthropathy and sickle cell disease.

Poststreptococcal reactive arthritis is diagnosed in patients who have an arthritis that is not typical of rheumatic fever but who have evidence of recent streptococcal infection. This condition is said to occur after a shorter latent period than rheumatic fever, is less responsive to NSAIDs, may be associated with renal manifestations, and evidence of carditis is usually not seen. The distinction between poststreptococcal reactive arthritis and rheumatic fever is unclear, and many would recommend that a diagnosis of poststreptococcal reactive arthritis not be made in populations in whom rheumatic fever is common. Even if the diagnosis is considered, it is appropriate to offer a period of secondary penicillin prophylaxis, as for episodes of acute rheumatic fever (ARF), in such populations.[23]

Carditis

Carditis is the most serious manifestation of rheumatic fever because it may lead to chronic RHD with its attendant complications of atrial fibrillation, stroke, heart failure, infective endocarditis, and death. In some patients the carditis may be asymptomatic and is detected during clinical examination of a patient with arthritis or chorea. The incidence of carditis during the initial attack of rheumatic fever varies from 40% to 91% depending on the selection of patients and whether the diagnosis is made on clinical assessment alone or combined with echocardiography.[23]

The incidence of carditis in rheumatic fever varies with the age of the patient. It is reported in 90% to 92% of children under age 3 years, in 50% of children age 3 to 6 years, in 32% of teenagers age 14 to 17 years, and only in 15% of adults with a first attack of rheumatic fever.[20] In a 1951 review of 1000 patients, 65% were diagnosed as having carditis (see Classic References, Bland and Duckett Jones), and in the 1987 report of a Utah outbreak in the United States, 91% had carditis when clinical examination was combined with echocardiography (see Veasy).

The symptoms and signs of carditis depend on whether there is involvement of the pericardium, myocardium, or heart valves. The clinical diagnosis of carditis is based on the detection of an organic murmur that was not previously present (to indicate endocarditis), presence of a pericardial friction rub or signs of pericardial effusion (to indicate pericarditis), or cardiomegaly or congestive heart failure (CHF) (to indicate myocarditis).

Myocarditis in the absence of valvulitis is unlikely to be rheumatic in origin. It should be accompanied by an apical systolic or basal diastolic murmur. Patients with myocarditis may develop cardiomegaly and CHF, which may be severe and life threatening. Myocardial damage may manifest with electrocardiographic changes, which include varying degrees of heart block. Patients with first-degree heart block are usually asymptomatic. Patients with second- and third-degree heart block may be symptomatic and require a pacemaker if they develop CHF.[20] CHF may be caused by myocarditis or severe involvement of one or more heart valves. It occurs in 5% to 10% of the initial episodes and is more frequent during recurrences of rheumatic fever.

Pericarditis is associated with anterior chest pain (**see Chapter 83**), and a pericardial friction rub may be detected on clinical examination. Pericarditis can be detected clinically in about 10% of patients. The pericardial effusion may sometimes be large, but cardiac tamponade is rare, and constrictive pericarditis does not occur.

The most common valvular lesion is mitral regurgitation causing an apical pansystolic murmur. Aortic regurgitation is less common. Stenotic lesions are uncommon in the early stages of the disease, but a transient apical mid-diastolic murmur (Carey-Coombs) may occur in association with the murmur of mitral regurgitation. In patients with a history of previous RHD, a change in the character of the murmurs or the appearance of a new murmur will indicate the presence of acute rheumatic carditis.

Echocardiography is more sensitive and specific than cardiac auscultation for the detection of acute rheumatic carditis, such that it is recommended that all patients with suspected or definite rheumatic fever should undergo echocardiography[24] (see Classic References, Vasan). **Table 74.1** outlines the minimum echocardiographic criteria of the World Heart Federation for the diagnosis of pathologic regurgitation caused by rheumatic valvulitis.[25] The advent of portable echocardiography has increased the availability of cardiac ultrasound to many people in developing countries, resulting in its increasing use in screening for subclinical rheumatic heart valve disease.

TABLE 74.1 World Heart Federation Minimum Echocardiographic Criteria for Diagnosis of Pathologic Valvular Regurgitation Caused by Rheumatic Carditis

Pathologic Mitral Regurgitation*
1. Seen in at least two views.
2. In at least one view, jet length is ≥2 cm.†
3. Peak velocity ≥3 meters/second.
4. Pansystolic jet in at least one envelope.
Pathologic Aortic Regurgitation*
1. Seen in at least two views.
2. In at least one view, jet length is ≥1 cm.†
3. Peak velocity ≥3 meters/second.
4. Pandiastolic jet in at least one envelope.

*All four Doppler criteria must be met.
†A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red) on nonmagnified (nonzoomed) images.
From Reményi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease: an evidence-based guideline. Nat Rev Cardiol 2012;9:297-309.

Sydenham Chorea

Chorea may be the only presenting manifestation of rheumatic fever. It is more common in females, and after puberty there is an even greater female predominance. The latent period between the episode of streptococcal pharyngitis and the development of chorea is considerably longer (6 to 8 weeks) than for arthritis and carditis. Chorea is characterized by the presence of involuntary, purposeless, jerky movements of the hands, arms, shoulders, feet, legs, face, and trunk associated with hypotonia and weakness. The purposeless movements interfere with voluntary activity and disappear during sleep. Initially, chorea may be confined to the face or one arm and sometimes may be unilateral (hemichorea).

Patients also show motor impersistence by intermittently, involuntarily withdrawing the tongue when attempting to protrude it for 30 seconds (jack-in-the-box tongue). Motor impersistence may also be demonstrated by asking the patient to squeeze the examiner's hand. This results in repetitive, irregular squeezes called the "milking sign." Emotional lability manifests in personality changes, with inappropriate behavior, restlessness, outbursts of anger or crying, and learning difficulties.

Chorea may last for 1 week to 2 years but usually lasts 8 to 15 weeks. When chorea occurs alone, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and streptococcal antibody titers may be normal because of the long latent period and resolution of the original infection. Chorea does not occur simultaneously with arthritis but may coexist with carditis. Some patients with chorea may have a cardiac murmur, whereas others may only later manifest involvement of the mitral valve.

Sydenham chorea with motor tics may overlap with the involuntary jerks of Tourette syndrome. The term *pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections* (PANDAS) has been used for a subgroup of children with tic or obsessive-compulsive disorders triggered by GAS infection with no associated cardiac valve damage.[26] However, the evidence supporting the existence of PANDAS as a distinct clinical entity has been questioned, leading to the recommendation that, in populations at high risk for rheumatic fever, clinicians should rarely, if ever, make a diagnosis of PANDAS; rather, they should err on the side of diagnosis of rheumatic fever and secondary prophylaxis.[24]

Subcutaneous Nodules

The subcutaneous nodules of rheumatic fever resemble the nodules of rheumatoid arthritis and may be detected over the occiput, elbows,

knees, ankles, and Achilles tendons. In rheumatic fever the nodules around the elbow tend to occur over the olecranon, whereas rheumatoid nodules tend to occur more distally along the extensor aspect of the upper forearm. They are usually firm, painless, and freely movable over the subcutaneous tissue. The nodules vary in size from 0.5 to 2 cm and tend to occur in crops (**Fig. 74.5**). They are usually smaller, more discrete, and less persistent than rheumatoid nodules. The nodules were detected in only 1.5% of patients in a series of 786 patients, although a higher prevalence was reported in earlier studies.[20] Nodules are usually seen in children with prolonged active carditis rather than in the early stages of rheumatic fever. They may persist for a few weeks but seldom more than 1 month. Multiple crops of nodules may be related to the severity of the rheumatic carditis.

Erythema Marginatum

Erythema marginatum is a less common manifestation of rheumatic fever and occurs on the upper arms or trunk but not the face (**Fig. 74.6**). It has a characteristic appearance and is therefore helpful in the diagnosis of rheumatic fever but is not pathognomonic of the disease. The rash is evanescent, pink, and nonpruritic. It extends centrifugally while the skin at the center returns to normal and has an irregular, serpiginous border. The rash may also become more prominent after a hot shower. Erythema marginatum usually occurs in patients with carditis and may occur early or later in the course of the disease.

Other Manifestations

The temperature is usually raised during attacks of rheumatic fever and ranges from 38.4°C to 40°C. When temperature is used as a minor diagnostic criterion, however, a cutoff value of higher than 37.5°C would allow the diagnosis of fever in 90% of suspected cases of rheumatic fever in endemic communities, such as indigenous Australians. The temperature usually decreases within 1 week and rarely lasts more than 4 weeks.

Abdominal pain may be severe and may mimic acute appendicitis. Epistaxis was reported as a common manifestation in the past but is now uncommon. Rapid sleeping pulse rate, tachycardia out of proportion to fever, malaise, and anemia may be noted in patients with ARF. Rheumatic pneumonia is uncommon and is difficult to distinguish from pulmonary edema and other causes of alveolitis.

FIGURE 74.5 Subcutaneous nodules of rheumatic fever over the bony prominences of the elbow. (From Beerman, LB, Kreutzer J, Allada V. Cardiology. In Zitelli BJ, McIntire SC, Nowalk AJ, editors. Atlas of Pediatric Physical Diagnosis. 6th ed. Philadelphia: Saunders; 2012.)

FIGURE 74.6 Erythema marginatum in acute rheumatic fever. The pen mark shows the location of the rash approximately 60 minutes previously. (From Cohen J, Powderly WG. Infectious Diseases. 2nd ed. St Louis: Mosby; 2004.)

DIAGNOSIS

Although no specific clinical, laboratory, or other test exists to confirm conclusively a diagnosis of rheumatic fever, the diagnosis is usually made using the clinical criteria first formulated in 1944 by T. Duckett Jones. Since then the criteria have undergone multiple modifications, with the most recent revision by the American Heart Association (AHA) in 2015[13,27] (**Table 74.2**). The initial diagnosis of ARF is made if, in the presence of preceding GAS infection, two major criteria or one major and two minor criteria are present. The diagnosis of *recurrent* ARF requires two major, one major and two minor, or three minor criteria in the presence of preceding GAS infection. Evidence of preceding GAS infection, essential for the diagnosis, may be obtained from throat swab culture (only positive in approximately 11% of patients at diagnosis of rheumatic fever) or by demonstrating a rising titer of antistreptococcal antibodies, either antistreptolysin O (ASO) or anti–deoxyribonuclease B (anti-DNase B), or by a positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probability of streptococcal pharyngitis.[13,28]

There are three main changes in the 2015 revised Jones criteria. First, subclinical valvulitis detected by echocardiography (as defined

TABLE 74.2 2015 AHA-Revised Jones Criteria for Diagnosis of Rheumatic Fever*

MAJOR CRITERIA	
Low-Risk Populations	**Moderate- and High-Risk Populations**
Carditis (clinical or subclinical†)	Carditis (clinical or subclinical)
Arthritis (polyarthritis only)	Arthritis (including polyarthritis, monoarthritis, or polyarthralgia‡)
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
MINOR CRITERIA	
Low-Risk Populations	**Moderate- and High-Risk Populations**
Polyarthralgia	Monoarthralgia
Fever (≥38.5°C)	Fever (≥38°C)
ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL	ESR ≥30 mm in the first hour and/or CRP ≥3.0 mg/dL§
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

Joint manifestations are only considered in either the major or the minor category, but not in both categories in the same patient.
*Annual acute rheumatic fever (ARF) incidence of ≤2 per 100,000 school-aged children or all-age rheumatic heart disease (RHD) prevalence of ≤1 per 1000 people per year.
†Defined as echocardiographic valvulitis, as defined in Table 74.1.
‡Polyarthralgia should only be considered as a major manifestation in moderate- and high-risk populations after exclusion of other causes.
§C-reactive protein (CRP) value must be greater than the normal laboratory upper limit. In addition, because the erythrocyte sedimentation rate (ESR) might evolve during the course of ARF, peak ESR values should be used.

in **Table 74.1**) is accepted as a major criterion for the diagnosis of ARF in all patient populations. Second, there is recognition that the clinical utility of the Jones criteria is determined by the pretest probability and background disease prevalence in a population. To avoid overdiagnosis in low-incidence populations and underdiagnosis in high-risk populations, variability in applying diagnostic criteria in low-risk versus high-risk populations has been introduced in line with the Australian guidelines.[13,24] Low-risk communities are defined as having an ARF incidence of less than 2 per 100,000 school-aged children (usually 5 to 14 years old) per year, or an all-age prevalence of RHD of 1 or more per 1000 population per year. In moderate- to high-risk communities, monoarthritis and polyarthralgia have been added as major criteria to polyarthritis, and a temperature of 38°C and monoarthralgia are the revised minor criteria (**see Table 74.2**).

The addition of monoarthritis or polyarthralgia as a major criterion and the inclusion of a fever higher than 38°C and monoarthralgia as a minor criteria have increased the sensitivity of the modified Jones criteria in communities with hyperendemic levels of ARF.[24]

The 2015 Jones criteria also recognize the clinical entity of "possible" rheumatic fever. It is appropriate for clinical judgment to be applied in parts of the world where rheumatic fever remains common and where it is not possible to fulfill the Jones criteria because of a lack of laboratory facilities to conduct the recommended investigations of a patient with suspected rheumatic fever, as listed in **Table 74.3**.[23,24] When a diagnosis of possible rheumatic fever is made in a high-incidence setting, it is reasonable to consider offering 12 months of secondary prophylaxis, followed by reevaluation based on history, physical examination, and repeat echocardiogram.

TREATMENT

The aim of treatment of a proven attack of rheumatic fever is (1) to suppress the inflammatory response and thus minimize the effects of inflammation on the heart and joints, (2) to eradicate the GAS from the pharynx, (3) to provide symptomatic relief, and (4) to commence secondary prophylaxis.

TABLE 74.3 Investigations in Suspected Rheumatic Fever

Recommended for All Cases
White blood cell count
Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
Throat swab before giving antibiotics for GAS culture
Blood culture, if febrile
Antistreptococcal serology: both antistreptolysin O (ASO) and anti-DNase B titers (repeat after 10 to 14 days if first test is not confirmatory)
Electrocardiogram
Chest radiograph
Echocardiogram
Tests for Alternative Diagnoses, Depending on Clinical Features
Repeated blood cultures with temperature spikes if infective endocarditis is suspected
Joint aspirate for possible septic arthritis (microscopy and culture)
Copper, ceruloplasmin, antinuclear antibody, and drug screen for choreiform movements
Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis
Peripheral blood smear for sickle cell disease

GAS, Group A beta-hemolytic streptococci.
From RHD Australia (ARF/RHD writing group), National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. 2nd ed. Darwin, Australia: Menzies School of Health Research; 2012.

The longstanding recommendation of bed rest would appear to be appropriate mainly to lessen joint pain. The duration of bed rest should be individually determined, but ambulation can usually be started once the fever has subsided and acute-phase reactants are returning to normal. Strenuous exertion should be avoided, especially for those with carditis.

Even though throat swabs taken during the acute attack of rheumatic fever are rarely positive for GAS, it is advisable for patients to receive an intramuscular (IM) dose of benzathine benzylpenicillin (or erythromycin if allergic to penicillin). Although conventional, this strategy is untested. Thereafter, secondary prophylaxis should be commenced (see Classic References, Manyemba and Mayosi).

The choice of anti-inflammatory agent is among salicylates, NSAIDs, and corticosteroids. A systematic review of randomized controlled trials (RCTs) compared anti-inflammatory agents (e.g., aspirin, corticosteroids, immunoglobulins, pentoxifylline) with placebo or controls, or compared any of the anti-inflammatory agents with one another, in adults and children with rheumatic fever diagnosed according to the Jones or modified Jones criteria.[28] The presence of cardiac disease 1 year after treatment was the major outcome criterion selected. Eight RCTs involving 996 people were included. Several steroidal agents (corticotrophin, cortisone, hydrocortisone, dexamethasone, prednisone) and intravenous (IV) immunoglobulin were compared to aspirin, placebo, or no treatment in the various studies. Six of the trials were conducted between 1950 and 1965, one study in 1990, and the final study in 2001. Overall, there was no significant difference in the risk of cardiac disease at 1 year between the corticosteroid-treated and aspirin-treated groups (six studies, 907 participants; relative risk [RR], 0.87; 95% confidence interval [CI] 0.66 to 1.15). Similarly, use of prednisone (two studies, 212 participants; RR, 1.13; 95% CI 0.52 to 2.45) compared to aspirin did not reduce the risk of developing heart disease after 1 year. The three studies reporting adverse events all found substantial adverse events. Thus, there is little evidence of benefit from using corticosteroids or IV immunoglobulins to reduce the risk of heart valve lesions in patients with ARF.[28]

These trials may be criticized on at least two grounds. First, the method used to assess cardiac involvement was clinical, with the development or persistence of an apical systolic murmur the usual criterion. It could be argued that observer error and interobserver variability of clinical methodology could invalidate the results, and that the question should be reexamined using modern, noninvasive techniques such as echocardiography. It has been shown, however, that at least during the acute phase of the illness, transthoracic two-dimensional echocardiography with color flow imaging does not add significantly to the clinical evaluation of the degree of cardiac involvement. The second point relates to the duration of follow-up. Lack of clinical evidence of cardiac involvement at 1 or 2 years after the initial attack of ARF is no guarantee that the important sequelae of valvular incompetence or stenosis will not develop in the ensuing decades.

The appropriate dosages of anti-inflammatory agents are aspirin, 100 mg/kg/day in four or five divided doses, and prednisone, 1 to 2 mg/kg/day. The duration of therapy must be gauged from the severity of the attack, presence of carditis, and rate of response to treatment. Milder attacks with little or no carditis may be treated with salicylates for approximately 1 month or until inflammation has subsided, as assessed by clinical and laboratory evidence. More severe cases may require 2 to 3 months of corticosteroid therapy before this can be gradually weaned. Up to 5% of patients may still have rheumatic activity despite treatment at 6 months. Occasionally a "rebound" of inflammatory activity can occur when anti-inflammatory therapy is reduced and may require salicylate treatment.

In patients whose initial attack of rheumatic fever is inadequately treated, there is a high risk that the rheumatic activity will continue and result in valvular incompetence, most often of the mitral valve. The end result of an ongoing rheumatic process with deteriorating valvular function is heart failure. Experience has shown that in such cases, prompt surgical management is the sole option and can result in the survival of up to 90% of patients.[29] It has been suggested that the reduction in cardiac workload following valve surgery results in

a settling of the rheumatic process, similar to the beneficial effect observed for bed rest.[30]

PREVENTION

There are three levels of prevention of rheumatic fever: primordial prevention, based on removal of the social determinants of risk for rheumatic fever; primary prevention of the initial attack; and secondary prevention of recurrent attacks.

Primordial Prevention

Primordial prevention consists of measures to minimize future hazards to health and thus inhibit the establishment factors (environmental, economic, social, behavioral, cultural) known to increase the risk of disease. It addresses broad health determinants rather than preventing personal exposure to risk factors, which is the goal of primary prevention. In the case of rheumatic fever, the improvement of social conditions and increasing access to primary health care have been associated with a dramatic fall in the incidence of the disease even before the discovery of antibiotics (curve A, **Fig. 74.1**). Therefore the prevention of rheumatic fever primarily requires the improvement of socioeconomic status of people at high risk of developing rheumatic fever.

Primary Prevention

Antibiotic treatment of proven or presumed GAS pharyngitis is effective in reducing the attack rate of rheumatic fever by 70%. IM penicillin appears to reduce the attack rate by as much as 80%. There is one fewer case of rheumatic fever for every 50 to 60 patients treated with antibiotics.[11] **Table 74.4** presents the drug regimen of choice.[27]

The treatment of proven or presumed GAS pharyngitis is directed toward eradication of the bacteria from the upper respiratory tract. The infection can usually be eradicated by a single IM injection of benzathine benzylpenicillin or by 10 days' treatment with oral penicillin.[11] Although the use of IM penicillin to prevent rheumatic fever is supported by clinical trials, few trials have been done to test the efficacy of oral penicillin for the primary prevention of rheumatic fever. However, there is resistance to using IM penicillin in some developing countries because of the perceived higher risk of anaphylaxis and the dangers associated with the potential reuse of needles. Concerns over safety of IM penicillin have resulted in government orders prohibiting penicillin injections in hospitals and clinics. Government regulations in response to some of these concerns are warranted, particularly in the area of infection control by preventing needle reuse. However, with respect to the dangers of anaphylaxis, more than 60 years of experience with penicillin has shown that, although toxic reactions to IM penicillin have been reported, severe reactions are exceedingly rare, especially in children. Therefore, when given under sterile conditions with an appropriate injection technique, concern regarding the use of parenteral penicillin is unwarranted.[11]

Three major controversies surround the primary prevention of rheumatic fever. The first concerns the role of active ascertainment of cases of sore throat in school-based primary prevention programs. This strategy has been tested in a cluster randomized trial of 53 schools (approximately 22,000 students) from a high-incidence rheumatic fever setting (approximately 60/100,000/year) in Auckland, New Zealand.[31] The control group received routine general practice care. The intervention was a school-based sore throat clinic program with free nurse-observed oral penicillin treatment of GAS pharyngitis. This study involving 86,874 person-years showed no significant reduction of rheumatic fever in the school-based sore throat clinic programs.

The second controversy relates to the utility of primary prevention as a public health measure for the prevention of rheumatic fever.[4] Although there are no RCTs of this strategy, there are several examples of the successful application of primary prevention in the context of a comprehensive public health program for the prevention of rheumatic fever in Cuba, Costa Rica, and the French islands of Martinique and Guadeloupe (curve C, **Fig. 74.1**).[4,16]

Third, the cost-effectiveness of primary prevention as a public health strategy for the prevention of rheumatic fever has been questioned.[4,8] A study conducted in South Africa shows that a strategy of using a clinical decision rule to diagnose GAS pharyngitis without culturing and providing treatment with a single IM injection of penicillin is a cost-effective strategy for the primary prevention of rheumatic fever in a high-risk community.[32] A strategy of culturing all children is prohibitively expensive. Taken together with the clinical trial evidence,[11] the evidence suggests that primary prevention by treatment of symptomatic cases of GAS pharyngitis diagnosed on clinical grounds may be a cost-effective public heath strategy for the prevention of rheumatic fever in the context of a comprehensive national program for prevention of the disease.[27]

Secondary Prevention

A systematic review of the effectiveness of antibiotics in the secondary prevention of rheumatic fever shows two principal findings (see Classic References, Manyemba and Mayosi). First, the evidence from clinical trials is strongly in support of the superiority of IM compared to oral penicillin in the prevention of rheumatic fever recurrences. Second, more frequent injections are more effective in preventing rheumatic fever recurrence than injections every 4 weeks. The evidence is strong for injections every 2 weeks, with an almost 50% reduction in the risk of rheumatic fever recurrence compared to injections every 4 weeks. The evidence for injections every 3 weeks is less strong and may be even weaker if the analysis takes into account the systematic error introduced by inadequate randomization and allocation concealment in the studies. Despite this evidence, the World Health Organization (WHO)[27] recommends intervals of 3 to 4 weeks for the secondary prevention of rheumatic fever (**Table 74.5**).

Recommendations regarding the duration of secondary prophylaxis are largely empiric and based on observational studies. The duration of prophylaxis should be individualized and take into account the socioeconomic conditions and risk of exposure to GAS for that patient. Individuals who have had carditis, with or without valvular involvement, are at higher risk for recurrent attacks and should receive prophylaxis well into adulthood and perhaps for life. If valvular heart disease persists, prophylaxis should be lifelong. Patients who have not had rheumatic carditis may receive prophylaxis until 21 years of age or 5 years after the last attack[27] (**Table 74.6**).

TABLE 74.4 Drug Regimen of Choice for Primary Prevention of Rheumatic Fever

ANTIBIOTIC	ADMINISTRATION	DOSE
Benzathine benzylpenicillin	Single intramuscular injection	1.2 million units; 50% if <30 kg in weight
Phenoxymethylpenicillin (penicillin VK)	Oral for 10 days	250-500 mg three times daily for 10 days
Erythromycin ethylsuccinate	Oral for 10 days	Varies with the formulation

Data from World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert panel. WHO Technical Report Series No. 923. Geneva: WHO; 2004.

TABLE 74.5 Drug Regimen of Choice for Secondary Prevention of Rheumatic Fever

ANTIBIOTIC	ADMINISTRATION	DOSE
Benzathine benzylpenicillin	Single intramuscular injection every 3-4 weeks	For adults and children ≥30 kg in weight: 1,200,000 units For children <30 kg in weight: 600,000 units
Penicillin V	Oral	250 mg twice daily
Sulfonamide*	Oral	For adults and children ≥30 kg in weight: 1 g daily For children <30 kg in weight: 500 mg daily
Erythromycin	Oral	250 mg twice daily

*Including sulfadiazine, sulfadoxine, and sulfisoxazole.
Data from World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert panel. WHO Technical Report Series No. 923. Geneva: WHO; 2004.

TABLE 74.6 Duration of Secondary Prophylaxis for Rheumatic Fever

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Patient without proven carditis	For 5 years after last attack or until 18 years of age (whichever is longer)
Patient with carditis (mild mitral regurgitation or healed carditis)	For 10 years after last attack or at least until 25 years of age (whichever is longer)
More severe valvular disease	Lifelong
After valve surgery	Lifelong

Data from World Health Organization. Rheumatic fever and rheumatic heart disease: report of a WHO expert panel. WHO Technical Report Series No. 923. Geneva: WHO; 2004.

FUTURE PERSPECTIVES

The key challenge to the control of rheumatic fever is related to the identification and removal of barriers to the translation of existing knowledge into policy, programs, and practice. There is good evidence that a comprehensive national program that includes primary and secondary prevention interventions is effective in reducing the incidence of rheumatic fever and rheumatic heart disease in endemic countries.[4] Therefore a need exists for cardiovascular practitioners and other partners in endemic countries to work with their ministries of health to establish national public health programs of prevention, as recommended by WHO in 2001.[27]

The efforts to prevent and control rheumatic fever will be facilitated by improvement of access to and development of better formulations of penicillin, identification of the 3% to 5% of individuals with genetic susceptibility to rheumatic fever, and development of an effective vaccine for GAS infection. Benzathine penicillin is a WHO essential drug, but it is not available to all who need it in affected countries. Furthermore, the current formulations of injectable penicillin require frequent administration and follow-up, which impose a heavy burden on fragile primary health care systems in developing countries. Therefore it is necessary not only to improve access to high-quality benzathine penicillin, but also to develop new, long-acting formulations that will improve adherence and the effectiveness of prevention programs.

An understanding of the molecular genetic mechanisms underlying host susceptibility can provide important insights into the pathogenesis of rheumatic fever, which in turn can inform diagnosis, new treatments, and vaccine development. Currently, the syndromic Jones criteria are not very sensitive or specific in countries with a high incidence, and a test for susceptibility may increase specificity. The identification of all genetic susceptibility factors for rheumatic fever through whole-genome analysis may lead to the development of a useful predictive genetic risk score for the disease and an improvement of the Jones criteria in the future.[14]

A safe, effective, and affordable vaccine designed to prevent GAS infections could have a major impact on the health of millions of people at risk of developing rheumatic fever. Research over several decades has yielded a number of different candidate vaccines in various stages of preclinical and clinical development. Vaccine development efforts have been hampered by several obstacles, which can be overcome through global collaborative efforts to identify key activities and secure financial resources that will accelerate the process, leading to the successful introduction of a safe, effective vaccine for the entire world.[33]

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