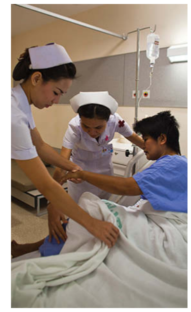

Chapter 11

Structural Heart Diseases

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INTRODUCTION

Structural heart diseases constitute a large proportion of the burden of cardiovascular disease in low- and middle-income countries (LMICs). Some conditions, such as rheumatic heart disease (RHD) and Chagas disease (CD), are associated with poverty and are preventable. Congenital heart disease (CHD), in contrast, is prevalent in all regions, but treatment is more readily available in higher-income countries. All structural heart diseases have a progressive course in the absence of prevention or surgical treatment.

This chapter summarizes the key clinical and public health issues around three key groups of structural heart disease: major congenital heart defects, RHD, and CD. Although advanced surgical care for these conditions is a rapidly evolving topic, this chapter emphasizes the importance of primary prevention and early detection, which are the missing links in many programs. These activities have particular relevance in resource-constrained settings, where access to advanced surgical and interventional care is not feasible.

CONGENITAL HEART DISEASE

The Condition

Incidence and Natural History

CHD is the most common single congenital anomaly. The overall incidence of CHD is approximately 8–10 per 1,000 live births; 5–6 per 1,000 require specialized interventions, and approximately 50 percent of these are patients during the neonatal or early infancy period of critical CHD (Hoffman and Kaplan 2002). Systematic efforts have been made to determine the burden of CHD in selected LMICs (Saxena and others 2015). Vaidyanathan and others (2011) reported 425 babies (7.75 percent) with CHD of the 5,487 consecutive newborns screened at a community hospital in Kerala, India. Of these, 17 (0.31 percent) had major CHD that was likely to require correction through heart surgery or catheter procedure; the rest had minor lesions, most of which normalized without intervention by age six weeks (Vaidyanathan and others 2011). The incidence among live births in China was similar to that in high-income countries (HICs)—8.2 per 1,000 live births—although a much higher incidence was seen among stillbirths, 168.8 per 1,000 (Yang and others 2009).

Most forms of CHD in HICs are also encountered in LMICs, but the outcomes vary in LMICs depending on the availability of facilities and expertise (Kumar 2003; Kumar and Shrivastava 2008). Table 11.1 summarizes the natural history and modified natural history, following surgery or catheter intervention, of common forms of CHD.

Global Burden and Geography

The World Health Organization (WHO) estimates that 230,000 deaths or 20.3 million disability-adjusted life-years (DALYs) from CHD occurred globally in 2000 and 234,000 deaths or 19.8 million DALYs occurred in 2012, corresponding to 0.4 percent of total deaths and

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Table 11.1 Broad Categories of Congenital Heart Disease, Classified According to Natural History

Broad category	Implications for survival and treatment	Examples[a]
Critical CHD	Incompatible with survival without specific intervention in newborn period or early infancy	Transposition of the great arteries, obstructed TAPVC, duct-dependent pulmonary or systemic circulation
Major CHD	Intervention is required, often in early infancy, for optimal long-term outcome	TOF, DORV, large VSD and PDA, complete atrioventricular canal, truncus arteriosus, aorto-pulmonary window, single ventricle physiology, unobstructed TAPVC, ALCAPA, severe outflow tract obstructions
CHD that typically manifests at an older age	Diagnosis seldom made in early childhood; intervention required to prevent long-term sequelae in adulthood	Moderate or large ASD, some forms of coarctation, some patients with Ebstein's anomaly, relatively less severe forms of aortic and pulmonary valve stenosis, congenitally corrected transposition of the great arteries with intact ventricular septum
Minor CHD	Long-term, symptom-free survival can be expected without any specific intervention in most cases	Small left-to-right shunts (ASD, VSD, PDA), bicommissural aortic valve

Note: ALCAPA = anomalous coronary artery from pulmonary artery; ASD = atrial septal defect; CHD = congenital heart disease; DORV = double outlet right ventricle; PDA = patent ductus arteriosus; TAPVC = total anomalous pulmonary venous communication; TOF = tetralogy of Fallot; VSD = ventricular septal defect.
a. These examples are not a comprehensive list of conditions; many conditions are not listed. Numerous combinations are possible.

0.7 percent of DALYs in each year. The impact of the congenital anomalies varies by geographic region. They account for 510 DALYs per 100,000 population in the Middle East and North Africa, but only 260 DALYs per 100,000 population in East Asia and Pacific (WHO 2015).

Risk Factors

Genetic predisposition, in conjunction with environmental factors, appears to explain the occurrence of CHD. The recurrence risk in siblings of an affected individual is 1 percent to 6 percent when neither parent is affected (Burn and others 1998; Calcagni and others 2007); if more than one sibling is affected, this risk can increase to 10 percent (Nora and Nora 1988). Obstructive left-heart lesions generally have a higher risk of recurrence, compared with other forms of CHD (Lewin and others 2004); an estimated 20 percent of the first-degree relatives of patients with obstructive left-heart lesions may have undiagnosed CHD, such as bicuspid aortic valve (Kerstjens-Frederikse and others 2011). CHD has also been been associated with environmental factors such as folate deficiency, maternal diabetes, and use of specific medications or alcohol during pregnancy (Blue and others 2012). Table 11.2 summarizes the risk factors.

Trends

CHD is unlikely to be perceived as a pediatric health priority in regions with high infant mortality, defined as greater than 20 per 1,000 live births. However, as infant mortality from communicable diseases continues to decline in most regions, CHD is likely to emerge as a significant health problem among infants and newborns in regions witnessing rapid and substantial human and economic development (Boutayeb 2006). Furthermore, the number of children born with CHD in LMICs is several times that in HICs because of population size, and birth rates are higher in most LMICs because of the higher numbers of women of reproductive age and higher fertility rates compared to HICs (UN 2014).

Interventions, Platforms, and Policies

Relatively modest benefits can be achieved by antenatal prevention efforts, but most of the postnatal interventions for CHD, whether screening or treatment, imply some availability of advanced, specialized surgical care.

CHD Prevention

Only 20 percent of cases have an identifiable cause; multifactorial inheritance has been proposed for cases of unknown etiology (Blue and others 2012). Genetic counseling and better family planning measures can help prevent CHD, especially if multiple family members are affected and a specific, inheritable, genetic disorder is identified. Consanguinity is a challenging problem and can be approached through educational programs targeted to the regions and communities where it is more frequently prevalent (Stoll and others 1999). Folate deficiency, use of certain medications during pregnancy, maternal diabetes, and phenylketonuria are also modifiable risk factors. Despite the limited

Table 11.2 Etiology of CHD: Prenatal Exposure to Acquired Factors

Risk factors	Associations with CHD
Diabetes and obesity	Various forms of CHD are linked with maternal gestational and pregestational diabetes or obesity, including transposition of the great arteries, ASD, VSD, hypoplastic left heart syndrome, cardiomyopathy, and PDA.
Phenylketonuria	Phenylketonuria is associated with a more than sixfold increase in the risk of CHD, specifically VSD, TOF, PDA, and single ventricle.
Febrile illnesses in the first trimester	Any febrile illness during the first trimester of pregnancy may result in a twofold increase in the risk of CHD.
Rubella	Specific cardiac manifestations of rubella embryopathy include PDA, pulmonary valve abnormalities, peripheral pulmonary stenosis, and VSD.
Epilepsy	The association may be a result of the risk of CHD from anticonvulsant medications.
Lupus (apart from typical symptoms of SLE, it may be useful to ask for history of previous abortions)	Maternal SLE is associated with risk of complete heart block in the offspring.
Vitamin deficiency	Multivitamin supplements, including folic acid derivatives, have been shown to protect against occurrence of CHD; multivitamins may reduce the risk of CHD associated with febrile illnesses in the first trimester.
Alcohol consumption	Muscular VSD
Maternal use of folate	Decreased risk of conotruncal anomalies
Prenatal exposure to medications in the first trimester, including anticonvulsants, NSAIDs, trimethoprim-sulphonamide, thalidomide, and vitamin A cogenors	Ebstein's anomaly, VSD, and ASD

Source: Blue and others 2012.
Note: ASD = atrial septal defect; CHD = congenital heart disease; NSAIDs = nonsteroidal anti-inflammatory drugs; PDA = patent ductus arteriosus; SLE = systemic lupus erythematosus; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

and inconclusive evidence, several general recommendations can be made for women during early pregnancy (Blue and others 2012):

- Daily folic acid and vitamin B12 supplementation in the preconception and periconception period
- Completion of rubella vaccination before pregnancy
- Optimal management of metabolic disorders, such as diabetes and phenylketonuria, before and during pregnancy
- Avoidance of medication associated with CHD before and during pregnancy, if possible.

CHD Screening

Prenatal diagnosis and postnatal screening protocols have helped in the early detection of CHD, especially those cases with critical duct-dependent lesions in HICs. In most LMICs, however, timely diagnosis of CHD is uncommon, and late presentation is the norm. Critical CHD may first manifest with hypoxemia, hypotension, or both and is frequently misdiagnosed as neonatal sepsis or pneumonia (Saxena 2005). Many pediatricians and primary care providers in LMICs do not regularly consider CHD to be a significant cause of neonatal and early infant morbidity and mortality, and intense targeted education and awareness are needed.

The relatively low overall prevalence of CHD and low positive predictive value of screening tests should be considered when evaluating whether to implement a screening program (Zühlke and Vaidyanathan 2013). Screening can be accomplished prenatally using fetal echocardiogram or in newborns using physical exam and pulse oximetry.

Prenatal Screening. Fetal echocardiography is often used to screen for CHD after 14–16 weeks gestation and is best suited for relatively severe forms of CHD. The test is time consuming, and accuracy is considerably influenced by operator expertise and quality of equipment (Sharland 2010), which are low in many LMICs. Nuchal translucency seen on first trimester antenatal ultrasound (appearing as a collection of fluid under the skin behind the fetal neck) may be an alternative screening test (Hyett and others 1999), but its sensitivity is low and its utility is probably limited (Makrydimas, Sotiriadis, and Ioannidis 2003). The treatment options in the event of a positive screening test are also limited. Termination of pregnancy may be an option in countries where it is legally permissible and screening is initiated before 20–24 weeks of gestation. Screening beyond the 20–24 week limit implies the capacity to refer patients to deliver at a center with a comprehensive pediatric heart program. Early referral for delivery overcomes the logistical challenges of transporting a newborn with CHD. Improved postnatal outcomes in prenatally diagnosed cases of CHD have not been consistently demonstrated (Sharland 2010).

Neonatal Screening. The identification of critical CHD soon after birth could substantially reduce mortality, but babies with critical CHD are not always immediately symptomatic. Early postnatal pulse oximetry has a higher sensitivity and specificity than clinical examination for detecting CHD (Vaidyanathan and others 2011). A meta-analysis of screening studies from HICs demonstrated that pulse oximetry was 76.5 percent sensitive and 99.9 percent specific for CHD (Thangaratinam and others 2012); however, the positive predictive value of screening in LMICs is poorly understood. Studies of pulse oximetry screening in resource-limited settings have yielded disappointing results (Saxena and others 2015; Vaidyanathan and others 2011).

Although physical examination has low sensitivity and specificity, one study demonstrated several findings that could identify patients with CHD (Vaidyanathan and others 2011). In these cases, follow-up examination is required at six weeks of life because certain defects—such as large ventricular septal defect and patent ductus arteriosus—can only be detected at that time. To date, routine physical examination screening programs in LMICs have not been evaluated.

Finally, while routine screening echocardiograms for all newborns is impractical, the use of echocardiography has value in cases where pulse oximetry or clinical examination suggests a higher than usual probability of CHD. Unfortunately, the barriers to widespread availability of echocardiography include high equipment costs and limited operator expertise (Kumar and Shrivastava 2008).

Screening of Infants and Toddlers. Screening modalities have not been systematically evaluated in this age group. Perhaps the best opportunity for screening for CHD is during routine immunization. A combination of clinical examination and pulse oximetry can be considered in this age group. It may be necessary to develop a simple clinical protocol and then validate it (Directorate General of Health Services 2006).

Screening of School Children. Cardiac auscultation is likely to be the most practical strategy for screening school children given that the utility of pulse oximetry in this group is very limited. CHD screening can potentially be integrated with screening for RHD, undernutrition, obesity, and hypertension (Thakur and others 1997). Children who are underweight and those with limited physical capacity need to be reevaluated, and the capacity to refer for confirmatory echocardiography is required for suspected cases.

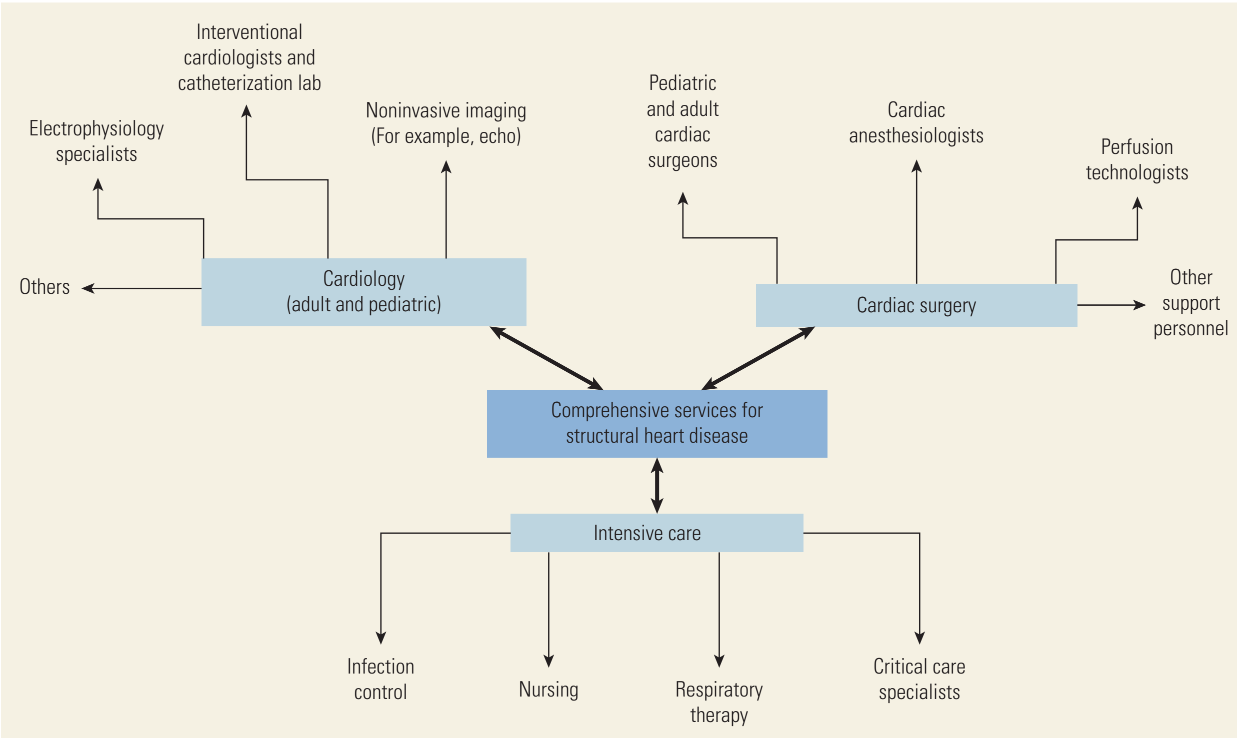
CHD Care and Treatment: Curative and Palliative

Management of CHD requires the building of surgical programs (figure 11.1) and skill sets that take decades to develop. Comprehensive pediatric heart care with facilities to treat even the most complicated lesions, however, is realistic only in selected centers in LMICs, usually limited to large cities (Kumar and Shrivastava 2008). Most LMICs have varying degrees of resources for treatment. These limitations apply to treatment of cases identified by screening, so consideration needs to be given to treatment availability before initiation of a new screening program. Furthermore, identification of a large number of CHD cases by screening will put additional pressure on specialized centers in LMICs to expand care.

Depending on the type of defect, surgical procedures are designed to either restore normal anatomy or physiology (or both) or palliate by improving physiology. The latter is more realistic for severe defects that lead to single ventricle physiology. The majority of CHDs require open-heart cardiac surgery, although increasing numbers of patients are being managed using catheter-based procedures. The cost of surgical interventions increases incrementally as CHD becomes more complex, and outcomes are often less than ideal. Many CHDs require multiple operations, often into adolescence or adulthood. In most cases, surgical intervention requires lifelong medical supervision to monitor for potential complications (Zühlke, Mirabel, and Marijon 2013).

Several new pediatric heart programs have been established in LMICs, such as in China, India, and Vietnam, and increasing numbers of heart operations and catheter interventions are being performed. Still, few comprehensive pediatric heart centers with the capability for infant and newborn heart surgery exist in LMICs; many of these centers, especially in India, are in the private sector and financially out of the reach of average families (Kumar and Shrivastava 2008; Saxena 2005). Existing centers are clustered in selected cities and regions with relatively better human development indices, and many children in Asia, Africa, and South America have no access to pediatric heart care (Zühlke, Mirabel, and Marijon 2013).

Figure 11.1 Organization of Resources Needed to Provide Surgical Care for Structural Heart Diseases



Source: Kumar and Shrivastava 2008.

Early initiation of treatment for children with CHD is widely recommended, but it is unrealistic in many LMICs, where treatment strategies and thresholds are significantly restricted. Palliation as the final path or as a bridge to complete repair at an older age may be the only realistic option in centers with limited resources (Kumar and Tynan 2005; Pinto and Dalvi 2004). Surgery may be offered as an alternative to the less invasive option of catheter closure of heart defects because of the cost of imported hardware (Kumar and Tynan 2005; Vida and others 2006).

Summary of Costs and Cost-Effectiveness of CHD Interventions

Cost of CHD Care

By means of semistructured interviews, Raj and others (2015) explored the direct and indirect expenses, sources of financing, and perceived financial stress of surgery for CHD on 464 Indian families whose children underwent surgery. They found that the surgery imposed a substantial economic burden on the health care infrastructure and affected families. The mean hospital expenses for the admission and surgery (including indirect costs to the family) accounted for an average of 0.93 (interquartile range 0.52–1.49) times the annual family income of patients (Raj and others 2015). Selected centers in LMICs have developed low-cost alternatives to expand the capacity to treat patients. These approaches include reuse of hardware (Kumar and Tynan 2005), development of novel devices and surgical prosthetics (Bhuvaneshwar and others 1996), and alternatives to the cardiopulmonary bypass circuit (Kreutzer and others 2005; Rasheed and others 2014).

Cost-Effectiveness of CHD Screening

Most cost-effectiveness analyses of CHD screening have been conducted in HICs and the results do not appear to be cost-effective using acceptability thresholds in LMICs. Modeling studies based in the United Kingdom and the United States have demonstrated that screening would generate more false than true positives and would only avert a handful of deaths annually, with incremental cost-effectiveness ratios (ICERs) exceeding US$40,000 per life year gained (Peterson and others 2013; Roberts and others 2012). Universal newborn oximetry screening is recommended in many HICs (Thangaratinam and others 2012); however, cost-effectiveness data from

LMICs are sparse, and published HIC ICERs would not be "acceptable" in LMICs. Furthermore, given the poor sensitivity and positive predictive value of the test in resource-limited environments (Vaidyanathan and others 2011), it is unclear that universal pulse oximetry screening can be recommended in LMICs.

CHD Programs in Low- and Middle-Income Countries

A Guatemalan experience demonstrates how a successful CHD program can be developed in a low-resource setting (Larrazabal and others 2007). The key aspect of the program was the creation of a self-sustaining endowment fund to support the cost of care, since 95 percent of patients required subsidized care. Monetary donations were collected through the Friends of Aldo Castenada Foundation. Individuals invested in stocks and company shares, and the interest returns on these investments were placed back into the endowment fund. The goal was to let the interest money accumulate. This fund was then used to share the cost of care with government-subsidized insurance and patient copays.

Bakshi and others (2007) reported that accumulative experience led to satisfactory neonatal CHD surgical outcomes in a center in southern India. Postoperative mortality decreased from 21.4 percent to 4.3 percent, although the prevalence of postoperative infections remained high. Similarly, the experience of the Amrita Institute of Medical Sciences in Kochi, India, has demonstrated that developing a pediatric heart center in a low-resource setting is feasible and can provide high-quality surgical care (Reddy and others 2015).

CHD Conclusions and Recommendations

Congenital heart disease contributes significantly to morbidity and mortality among children in LMICs. CHD is likely to surface as a pediatric health priority in many regions in the near future because of declining mortality from infectious diseases. Unfortunately, routine screening for CHD before or shortly after birth may not be realistic in many countries, and access to surgical care is limited, even for existing cases. Despite the limited and inconclusive evidence, a few general recommendations can be made:

- *Address modifiable risk factors for CHD whenever possible.* Several of these risk factors are routinely addressed by high-quality prenatal care—for example, folate supplementation, education about teratogens, and management of maternal weight and gestational diabetes—and investment in prenatal care can be a first step to addressing CHD in the absence of treatment options.
- *All countries can begin to consider building capacity for the treatment of CHD.* It may not be possible to meet the ideal requirement of one center per 5 million population (Davis and others 1996), but a limited number of regional centers could develop expertise in advanced CHD care and training. These centers do need to include investments in nonsurgical physician expertise, such as cardiovascular imaging and anesthesia, as well as nonphysician expertise, such as critical care nursing. Governments could subsidize such centers to serve as a source of local data on disease burden, educate local pediatricians to recognize CHD, and develop innovative and low-cost therapies and management protocols.
- *The decision to initiate universal screening for CHD is context and resource dependent.* The lack of an effective screening tool makes CHD screening difficult, and no cost-effectiveness studies have assessed CHD screening in LMICs. However, targeted efforts to improve awareness of early diagnosis and management among pediatricians are likely to improve detection in symptomatic infants and newborns. Cost-effectiveness studies of CHD screening could be considered in settings where surgical capacity exists.
- *Careful case selection needs to be part of any scale-up of surgical care for CHD.* The specific treatment strategy could be individualized, depending on resources, disease characteristics, comorbidities, and local medical expertise. Given the extraordinary clinical variety of CHDs, this task is likely to be daunting. Nevertheless, conditions such as ventricular septal defects, which can be corrected through a single operation, could receive higher priority; multistage palliative operations, such as those for hypoplastic left heart syndrome, could receive lower priority. No therapy may be the only realistic option in settings with significant resource limitations. Although philanthropy or charity can provide substantial help in providing care to families who cannot afford such therapies, donor exhaustion makes such sources unreliable. Endowments-based charity accounts, which are self-sustaining, may be more beneficial.
- *Consideration should be given to financing of CHD diagnosis and treatment.* In LMICs, cardiovascular care, including CHD surgery, is infrequently covered by public finance or other subsidized insurance systems; the inclusion of CHD care may allow a larger proportion of affected children to benefit from definitive treatment. However, in countries with very constrained budgets, public finance may not be financially sustainable and could detract from more pressing priorities for universal coverage.

RHEUMATIC HEART DISEASE

The Condition

Pathogenesis and Natural History

RHD, a chronic inflammatory disease of the heart valves, is the result of untreated group A streptococcal throat infection (pharyngitis). The streptococcus produces an abnormal immune response in susceptible individuals, typically between the ages of 5 and 15 years. This immune response manifests as acute rheumatic fever (ARF), and severe and recurrent episodes of rheumatic fever (RF) increase the likelihood of heart valve damage (Marijon and others 2012). RHD remains the most common cause of acquired heart disease in children and young adults in LMICs (Carapetis and others 2005).

RHD classically presents as progressive shortness of breath between the ages of 20 years and 50 years. It is slightly more common in women than men; in many women, its first manifestation is during pregnancy as the physiologic stress on the heart increases (Sliwa and others 2010). The clinical period is preceded by a long latent and asymptomatic period, however—perhaps as long as 10 years—especially for well-tolerated patterns of valve disease (Marijon and others 2012). This latent period poses significant barriers to clinical screening and preventive treatment, because individuals are often otherwise healthy. Many patients first present for care in advanced heart failure or with other complications, such as heart valve bacterial infection (endocarditis) or stroke due to atrial fibrillation (Sliwa and others 2010).

Global Burden and Geography of RHD

RHD is the most common cause of valvular heart disease in LMICs. There were an estimated 372,000 deaths or 14.3 million DALYs from RHD globally in 2000 and 337,000 deaths or 12.0 million DALYs in 2012 (WHO 2015). Most contemporary reports on RHD have come from South Asia, the Pacific Islands, and Sub-Saharan Africa; many indigenous communities in Asia and Pacific show a high prevalence of ARF and RHD risk factors (Carapetis and others 2005; Omurzakova and others 2009). The burden of RHD as measured by prevalence is an active topic in the literature (Zühlke and Steer 2013). Studies using echocardiography-based methods of measuring prevalence in schoolchildren have demonstrated a 10-fold higher prevalence of valvular abnormalities, compared with prevalence reported using clinical diagnostic methods (Marijon and others 2007). Little is known about the natural history of these asymptomatic cases compared with the smaller number of symptomatic cases that have traditionally been reported (Zühlke and Mayosi 2013).

Risk Factors

The most important risk factor for ARF seems to be proximity to other individuals with streptococcal pharyngitis—a situation seen in overcrowded areas with inadequate sanitation, such as among the urban poor (Robertson and Mayosi 2008). Other risk factors that correlate with poverty include undernutrition, low maternal educational level, and unemployment (Longo-Mbenza and others 1998). In HICs, the incidence of ARF began to decline before the discovery of penicillin, and this observation has prompted the hypothesis that economic development and sanitation are as important as antibiotic treatment in eradicating RHD (Gordis 1985). Genetic factors also may increase the risk of ARF (Engel and others 2011), which helps account for the empirical observation that, at most, 3 percent to 5 percent of individuals with untreated streptococcal pharyngitis will develop ARF, and even fewer will progress to RHD (Michaud, Rammohan, and Narula 1999).

Trends

The burden of RHD in both deaths and DALYs appears to be declining, but newer methods of measuring prevalence may lead to revisions of these estimates. Nevertheless, the decrease in burden is consistent with overall trends in economic development and global health gains during the past two decades. The distribution of these health gains remains unclear, particularly among the poorest and most remote populations. For example, in 2005, mortality from RHD in rural Ethiopia was 12.5 percent per year (Gunther, Asmera, and Parry 2006). Finally, declining mortality rates imply an increasing prevalence and an increasing case load on health systems in LMICs.

Interventions, Platforms, and Policies

RHD Interventions

Primary Prevention. Table 11.3 summarizes the key points of intervention in the natural history of ARF and RHD, covering primary and secondary prevention, surgical treatment, and *primordial prevention,* the latter referring to measures that reduce the incidence of streptococcal transmission in the general population. Research on primary prevention conducted in the 1950s among American military recruits demonstrated that penicillin treatment of streptococcal pharyngitis could reduce the risk of ARF by about 80 percent (Robertson, Volmink, and Mayosi 2005). Although most of the effectiveness data on primary prevention are older and of lower quality, penicillin is widely regarded as the mainstay of prevention and remains in all major clinical guidelines (Marijon and others 2012).

Table 11.3 Major Categories of Interventions for the Prevention and Control of RHD

Intervention	Rationale	Estimated efficacy or effectiveness	Comments
Vaccination against group A streptococcus	Prevent streptococcal sore throat infection	100 percent (theoretical) efficacy at preventing strep throat and ARF or RHD	No vaccine has yet been developed to cover all major serotypes affecting LMICs.
Primary prevention of ARF with benzathine penicillin G	Prevent development of first episode of ARF	80 percent relative risk reduction	Most trials conducted in 1950s and 1960s in young American males.
Secondary prevention of ARF and RHD with benzathine penicillin G	Prevent recurrent episodes of ARF and recurrent and progressive heart valve damage	55 percent relative risk reduction (penicillin vs. control); 87 percent to 98 percent relative risk reduction (injectable versus oral penicillin)	Trials are generally of poor quality and heterogeneous methodology, making results difficult to extrapolate.
Surgical and percutaneous management of established RHD	Palliate cases of advanced RHD with heart failure	Variable effectiveness: Depends on severity of disease, number of heart valves involved, and surgical technique	No controlled trials comparing surgical treatment to no therapy or to medical therapy. Percutaneous treatment of mitral stenosis can be very effective in well-selected cases but generally requires surgical capacity as a backup.

Note: ARF = acute rheumatic fever; LMICs = low- and middle-income countries; RF = rheumatic fever; RHD = rheumatic heart disease.

Secondary Prevention. Early studies of individuals with a documented history of ARF demonstrated that regular secondary preventive therapy with penicillin—especially injectable benzathine penicillin—could reduce the risk of recurrent ARF and, by inference, RHD (Manyemba and Mayosi 2002). The rationale for secondary prevention is that it eliminates streptococcal colonization and thereby persistent subclinical inflammation and progressive valve damage (Majeed and others 1986). Sufficient evidence indicates that secondary prevention programs produce low rates of ARF recurrence in patients receiving continuous secondary prophylaxis. However, the quality of controlled studies is suboptimal, and it has been difficult to quantify the relationship between ARF recurrences averted and reductions in incident RHD (Manyemba and Mayosi 2002). Despite these evidence gaps, there is strong consensus globally that secondary prevention is effective and that further trials on its effectiveness would not be ethical.

Limitations of the Evidence for Prevention. From the policy standpoint, interpreting and applying the literature on primary and secondary prevention poses several challenges.

- The studies are all of poor quality and are more than 20 years old; nearly all were conducted in HICs. These trials used older formulations of penicillin that are no longer in widespread use, limiting the usefulness of these data in contemporary economic models.
- There is no evidence that primary or secondary prevention reduces RHD mortality, and no such trials are likely to be performed in children for ethical reasons.
- No studies have been conducted for secondary prevention in adults with ARF and RHD, who constitute the majority of cases today.
- An exclusive primary prevention strategy could miss a substantial proportion of cases because 50 percent to 75 percent of ARF cases may have no history of symptomatic pharyngitis.
- Adherence to a regimen of three- or four-weekly penicillin injections for secondary prevention is often difficult to achieve in practice (Gunther, Asmera, and Parry 2006; WHO 1992).
- Despite aggressive prevention efforts, many patients with established RHD require surgical intervention when valve dysfunction becomes severe and symptomatic (Zühlke and others 2015).

Cardiac Surgery. For individuals with established RHD, surgical and percutaneous techniques are available to repair, replace, or palliate damaged valves. The mitral valve is most commonly affected by RHD and is the most frequent target of surgical and catheter-based interventions; the aortic and tricuspid valves are also susceptible. In general, patients with more than one valve involved have a poorer prognosis, even with adequate access to surgery (Marijon and others 2012).

For patients with isolated mitral stenosis (narrowed mitral valve) and favorable valve characteristics, catheter-based dilation (percutaneous balloon valvulotomy) has become the treatment standard—at least in settings with access to state-of-the-art equipment and interventional cardiologists. However, percutaneous procedures should be performed in centers with cardiothoracic surgical expertise in case of complications (figure 11.1). An alternative to percutaneous valvulotomy is closed mitral valvulotomy, which can be performed by a general or cardiothoracic surgeon in a center with fewer resources.

For many LMICs, however, the scale-up of open-heart surgical services may be the most important option for patients with advanced RHD. Given the prevalence of unfavorable mitral stenosis, mitral incompetence (which cannot currently be treated by catheter-based methods), and multivalvular disease, most patients with RHD are not eligible for minimally invasive techniques and eventually require surgical valve replacement. Valve replacement is palliative rather than curative; most patients require lifelong anticoagulation and are exposed to high complication rates (Marijon and others 2012).

Primordial Prevention. A final intervention for RHD, although theoretical at present, is a vaccine against group A streptococcus—primordial prevention. Vaccine research and development has been ongoing for years, with promising results in select populations from phase II clinical trials (Bisno and others 2005). Unfortunately, the global distribution of streptococcal serotypes is very different from those investigated in clinical trials (Steer and others 2009); an array of serotypes—more than could feasibly have been included in any previously developed multivalent vaccine—have been implicated in ARF. Efforts are underway to ensure the development of a vaccine that will be effective in LMICs (Dale and others 2013).

RHD Delivery Platforms

The potential delivery platforms for RHD-related interventions can be classified as follows:

- Community-based efforts to educate children, parents, and educators about sore throat, ARF, and RHD
- Provision of primary and secondary prophylaxis in outpatient settings, primarily in primary care settings
- Third-level care at specialized or referral facilities that offer cardiology and cardiac surgery services.

Community-Based Primary and Secondary Prevention. Successful ARF and RHD programs have implemented a comprehensive approach that integrates community-based education and awareness with the scale-up of sore throat treatment to increase primary prevention and case finding of patients with ARF and RHD to build disease registers and increase secondary prevention. The WHO recommends a comprehensive approach to RHD control modeled after these types of programs (WHO 2004).

Unfortunately, as of 2012, ARF and RHD prevention had not been included in standard guidelines and protocols for child health, such as the Integrated Management of Childhood Illness program. This omission is partly because most child health programs focus on those under age five years, and streptococcal sore throat and ARF are uncommon in this group. Accordingly, although the RHD community has produced many resources for managing sore throat and developing secondary prevention programs (Wyber 2013), these resources have yet to be integrated with other child and adolescent health interventions. Partners in Health has developed an integrated model for noncommunicable diseases that includes RHD, factoring in such issues as registration, supply chain management, and adherence support at both first- and second-level hospitals (Partners in Health 2011). However, this model has not yet been applied in a broad range of settings.

Secondary Prevention Using Echocardiography. Following the publication of echocardiography screening studies (Marijon and others 2007), many research groups attempted to develop active case finding programs to increase secondary prevention using echocardiography in community and school settings.[1] This approach was adopted by the Stop RHD A.S.A.P. Programme at the University of Cape Town (Robertson, Volmink, and Mayosi 2006) and by similar programs in the South Pacific (Lawrence and others 2013). Controversy remains about the long-term impact and cost-effectiveness of these programs because the natural history of cases detected by echocardiogram—and the effectiveness of secondary prophylaxis in this group—is unknown (Zühlke and Mayosi 2013).

Surgical Care Platforms. Although some countries have the capacity for specialized surgical and catheter-based interventions, at least in urban centers, the ratio of the population to the number of centers is grossly inequitable; only a handful of centers exist in all of Sub-Saharan Africa other than South Africa (Zühlke, Mirabel, and Marijon 2013). Three models of initiatives have helped ameliorate this situation:

- Some well-selected cases are transferred for surgery on a philanthropic basis to Europe and the United States; a variant of this model is for visiting surgeons to set up temporary services in-country in conjunction with charitable organizations.[2]

- Using South-South collaboration, patients are referred to high-volume regional or continental centers, such as in India or Sudan.[3] Unfortunately, many countries have national referral boards that finance out-of-country transfers on an extremely limited basis, and these referrals are likely to be somewhat biased against the rural poor who are less likely to receive a diagnosis or to benefit from advocacy efforts.
- Lower-income countries start to build surgical platforms in their own countries (Binagwaho and others 2013), although this model can be resource intensive and may detract from other health priorities.

ARF and RHD Public Policies for Prevention and Control

The WHO's comprehensive set of guidelines on RF and RHD for LMICs (WHO 2004) recommended a package of several types of activities within an integrated RHD program (table 11.4). The evidence for these public health initiatives largely came from Latin America and the Caribbean during the 1970s and 1980s, when ARF was essentially eradicated and the prevalence of severe RHD was dramatically reduced (Bach and others 1996; Nordet and others 2008). Although the decline in ARF and RHD in most regions has tracked closely with social and economic development, the role of primordial measures—policies dealing with risk factors such as overcrowding, sanitation and hygiene, and poor nutrition—is unclear, yet is likely to be significant (Gordis 1985).

There have been recent efforts to develop policies for ARF and RHD prevention and control in Africa. A technical consultation initiated by the African Union in 2015 produced a set of seven key actions for ARF and RHD (Watkins, Zühlke, and others 2016). In addition to the elements recommended by the WHO (2004) report, this consultation stressed the need to ensure adequate supplies of high-quality penicillin, which has recently experienced poor availability globally. It also highlighted the many points of integration with reproductive and maternal health services and with other noncommunicable diseases. These recommendations have since been adopted in a resolution signed by all African heads of state, and implementation plans are currently being developed in collaboration with the WHO.

Table 11.4 Components of an Integrated Program on ARF and RHD Prevention and Control

Component activity	Elements	Comments
Planning phase	Establishment of a national advisory committee; assessment of disease burden; stepwise implementation, monitoring, and evaluation	Program should be multisectoral, engaging stakeholders in ministries of health and education, and streamlined into existing infrastructure.
Primary prevention	Training of health care providers to accurately detect and treat streptococcal pharyngitis; ensuring adequate supply of and affordability of penicillin	Most effective when the importance of primary prevention is integrated into a public education program.
Secondary prevention	Establishment of national, regional, and local disease registers; active case finding, surveillance, and follow-up of existing cases	Particular focus should be given to cases at risk of poor adherence to regular prophylaxis.
Provider training	Training health care workers on primary and secondary prevention as appropriate, as well as management of anaphylactic reactions to penicillin	Engagement of public health nurses is essential in areas with physician shortages.
Health education	Regular educational activities to be carried out in schools and using local and nationwide print and electronic media programs	Messaging should summarize importance of primary and secondary prevention, promote health-seeking behavior for sore throat, and encourage efforts to limit spread of infection.
Epidemiologic surveillance	Regular audits of disease registers and conduct of prevalence studies (resources permitting), including microbiological surveillance	Reports should note seasonal frequency, distribution of cases, and streptococcal serotypes implicated.
Community engagement	Major stakeholders include health and educational administrators, school teachers and school health services, and families of patients.	Active screening of school children for RHD may be indicated in high-prevalence settings.

Source: Adapted from WHO 2004.
Note: ARF = acute rheumatic fever; RHD = rheumatic heart disease.

Summary of Costs and Cost-Effectiveness of RHD Interventions

Economic Burden of RHD

Appropriate management of RHD involves access to primary as well as specialized care, and long-term use of medications; for many individuals, it also involves one or more major surgeries. RHD results in both direct and indirect losses in productivity due to chronic disability. Only one study of the economic impact of RHD in an LMIC was identified. This study, in Brazil, demonstrated high rates of health care utilization, school and work absenteeism, and direct medical costs of approximately US$151,300 per 100 patients annually (Terreri and others 2001).

Cost of RHD Interventions

Published estimates of RHD intervention costs to the health system are scarce. One study reported primary, secondary, and tertiary prevention costs to Pondicherry Union Territory, India (population 974,345), as totaling approximately US$6.2 million, US$5.0 million, and US$8.8 million, respectively (Soudarssanane and others 2007). Irlam and others (2013) gathered primary cost data as part of a clinical cost-effectiveness analysis of primary prevention strategies in South Africa. Watkins and others (2015) reanalyzed data from Cuba and found that a combined primary and secondary prevention program cost approximately US$0.07 per year per at-risk child ages 5–14 years. Finally, it should be noted that although the prevalence of RHD is thought to be highest in low-income countries, the direct cost of RHD to the health system is probably higher in middle-income countries, where tertiary cardiology and cardiac surgery services are available and are being widely provided for persons with RHD.

Cost-Effectiveness of Primary RHD Prevention

In low-prevalence settings with inexpensive throat culture media, the most cost-effective strategy for ARF prevention is to screen with a rapid antigen test and send positive screens for throat culture, withholding treatment unless throat cultures are positive (Shulman and others 2012). In contrast, Irlam and others (2013) evaluated a clinical decision rule developed for low-resource settings. They compared treat-all and treat-none strategies to five algorithms that combined decision-rule cutoffs, with or without culture. In their high-prevalence setting (15.3 percent streptococcal pharyngitis), the most cost-effective strategy was to treat individuals with a decision-rule score of two or higher, without microbiologic confirmation. The ICER for this approach was US$145 per quality-adjusted life year, and it dominated all other strategies up to a willingness-to-pay threshold of US$60,000. These results have yet to be replicated in other countries.

Cost-Effectiveness of Secondary RHD Prevention

The evidence for the cost-effectiveness of secondary prevention is based primarily on the results of a multicountry study conducted by the WHO in the late 1970s to scale up secondary prevention. Over 5,500 patient-years were observed in the study. The cost of secondary prevention resources was much lower than the averted cost of hospitalizations for recurrent ARF, making the program cost saving by definition (Strasser and others 1981).

Some studies have attempted to model the cost-effectiveness of echocardiography to identify RHD cases and scale-up of secondary prevention, compared with other primary and secondary prevention strategies (Manji and others 2013). However, these studies rely on natural history assumptions that have not been borne out by long-term follow-up of echocardiography screening studies (Zühlke and Mayosi 2013).

Comparative Cost-Effectiveness of RHD Interventions

Several studies provide insights into the tradeoffs between various prevention and treatment strategies.

- Watkins and others (2015) demonstrated that a comprehensive approach to ARF and RHD control in Cuba—including both primary and secondary prevention at the community level—was cost saving. However, much of the savings were from cardiac surgery costs averted, and these savings may not be relevant to a country without these high health system costs.
- Soudarssanane and others (2007) compared primary and secondary prevention and surgery as isolated interventions, measuring benefits as gains in labor productivity and monetary value of deaths averted in a benefit-cost framework. They cited benefit-cost ratios of 1.56 for primary prevention, 1.07 for secondary prevention, and 0.12 for surgery and argued that primary prevention was the most cost-effective of the three approaches.
- A similar approach, with a narrower cost-effectiveness framework, was used as part of the first Disease Control Priorities project (Michaud, Rammohan, and Narula 1999). The study compared the cost-effectiveness of a theoretical vaccine to primary, secondary, and tertiary strategies in low- versus high-endemicity settings. Secondary prevention dominated primary prevention and surgery, while a theoretical vaccine was probably cost-effective compared with secondary prevention. This study extrapolated cost data from the early 1990s and,

compared with more recent work, used fairly crude assumptions in the model (Irlam and others 2013).
- Watkins, Lubinga, and others (forthcoming) updated this analysis using contemporary data on disease epidemiology and costs as well as a lifetime horizon model. They found that, in a hypothetical African country, scale-up of primary prevention would be cost saving and secondary prevention would be very cost-effective, with ICERs less than per capita gross domestic product of LMICs in Sub-Saharan Africa. Scale-up of surgery by referral to international sites (for example, in India) could be cost-effective in some contexts, but building an in-country surgical center would probably not be cost-effective and would have a large budgetary impact.

However, building cardiac surgery capacity in low-resource settings might yield economies of scope and scale and educational output with regard to training surgeons and cardiologists; these are benefits that cannot be included in a narrow cost-effectiveness analysis around RHD. Accordingly, decisions about building cardiac surgery should ideally use a benefit-cost analysis approach that accounts for the added benefits outside of the domain of RHD.

RHD Conclusions and Recommendations

RHD remains one of the most important cardiovascular conditions globally. Public policies to address ARF and RHD need to balance the lower costs and higher benefits of preventing future cases of RHD with the ethical obligation to consider advanced medical and surgical treatment of existing cases. Policy decisions are context specific and often made in an environment of high uncertainty.

We make the following general recommendations for countries seeking to increase their capacity to address the challenges of ARF and RHD:

- *All countries in endemic regions could implement steps to measure and monitor the burden of ARF and RHD.* Vital statistics, disease notification systems, and disease registers can be important sources of data for tracking ARF and RHD at a local level, and notification and registries can support primary and secondary prevention efforts.
- *Primary prevention could be a high priority and could be integrated into existing child and adolescent health interventions.* The successful control of ARF and RHD in several Latin American countries was predicated on combining primary and secondary prevention within existing care delivery programs. Such programs are likely to be synergistic when combined with secondary prevention (Watkins and others 2015).
- *The foundation of secondary prevention could be passive case finding through disease registries.* Active case finding through echocardiography-based screening has not yet been demonstrated to improve clinical outcomes; it should only be considered in the context of a well-functioning disease registry with adequate rates of adherence.
- *All countries in endemic regions could assess capacity for scaling up surgical care.* Some countries may find that establishing a surgical center is cost-effective and can strengthen health services for other diseases. Others may continue to rely on philanthropic care. A third model, particularly for very poor nations in Sub-Saharan Africa, would be to strengthen referral pathways to regional centers of excellence and provide greater financial protection for patients and families in need. In all of these cases, given the impact of surgery on premature child and young adult mortality, provision of surgery will likely lead to a positive return on investment.

CHAGAS HEART DISEASE

The Condition

Pathogenesis and Natural History

CD is caused by infection with the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*), and runs through acute and chronic phases. Diagnosis in the acute phase is rare since most patients are asymptomatic or experience a nonspecific flu-like episode. After the acute phase, a latent or indeterminate form of the disease occurs in which patients also remain asymptomatic. When the determinate forms appear late in the natural history of the infection, chronic Chagas cardiomyopathy (CCC) is the most common and ominous form of the disease (Rassi, Rassi, and Marin-Neto 2010).

Organ damage during the acute phase is associated with high-grade parasitemia, intense tissue parasitism, and the immuno-inflammatory response to the parasite, mainly in the heart, gastrointestinal tract, and central nervous system. Although several mechanisms may contribute to the pathogenesis of CCC, the consensus is that parasite persistence and the parasite-driven immune response are key factors (Marin-Neto and others 2007) along with neurogenic depopulation caused by the parasite, which may trigger malignant arrhythmia and sudden death (Marin-Neto and others 1992).

Although patients with the indeterminate form of CD—including those with any abnormality on highly sensitive blood tests—have a good prognosis, epidemiological studies in endemic areas have shown that, in 1 percent to 3 percent each year, the disease evolves from the indeterminate to the determinate forms (Sabino and others 2013). Accordingly, even patients with the indeterminate form require yearly follow-up (Rassi, Rassi, and Marin-Neto 2010). Major risk factors for mortality in patients with CCC are clinical heart failure, cardiomegaly, left ventricular systolic dysfunction, and nonsustained ventricular tachycardia (Rassi, Rassi, and Marin-Neto 2009; Rassi, Rassi, and Rassi 2007). A risk score for predicting mortality in patients with CCC has been developed (Rassi and others 2006) and validated (Rocha and Ribeiro 2006).

Global Burden and Geography

CD accounted for 9,000 deaths and 571,000 DALYs in 2000 and 8,000 deaths and 528,000 DALYs in 2012 (WHO 2015). Despite a substantial reduction in the number of individuals infected with *T. cruzi* worldwide—from between 16 million and 18 million in the 1990s to between 8 million and 10 million in the mid-2000s—CD still represents the third-largest tropical disease burden, after malaria and schistosomiasis. Most infections occur through vector-borne transmission by Triatominae insects; transmission can also occur through blood transfusion, from mother to infant, by ingestion of food or liquid contaminated with *T. cruzi*, and rarely by organ transplantation and accidents among laboratory personnel who work with live parasites (Rassi, Rassi, and Marin-Neto 2010).

Formerly, the disease was confined to socially underdeveloped rural areas in almost all Latin American and the Caribbean countries. However, because of the migration from endemic countries, CD has become a potential public health problem in nonendemic regions, including Australia, Europe, Japan, and the United States (Schmunis 2007). Transmission risk in HICs occurs mostly through the nonvector mechanisms; these are becoming increasingly important even in endemic regions where recent vector transmission programs have been successful.

Interventions, Platforms, and Policies

CD requires interventions at multiple levels. Vector control and prevention of transmission from nonvectorial mechanisms are the two essential strategies aimed at primary prevention. Reduction of domiciliary vector infestation by spraying of insecticides, improvement in housing conditions, and education of individuals at risk are the key measures. Most national vector control programs in Latin America and the Caribbean have been initiated centrally and have involved three successive stages:

- Rapid and aggressive mass insecticide spraying
- Respraying of houses with residual infestation
- Subsequent community surveillance.

The classic example is the Brazilian experience during the 1970s and 1980s, which resulted in near eradication of the vector by the mid-2000s (Moncayo and Silveira 2009). These measures, coupled with serological screening of blood donors, have markedly reduced transmission of the parasite in many endemic countries (Rassi, Rassi, and Marin-Neto 2010). Additionally, trypanocide treatment before pregnancy has been demonstrated to prevent congenital transmission in affected women treated before they become pregnant (Fabbro and others 2014).

Secondary prevention includes screening and finding cases of *T. cruzi* infection at an early asymptomatic stage of the disease to offer specific therapy. The mainstay of secondary prevention is treating patients with the indeterminate form of the disease with a trypanocidal agent such as benznidazole or nifurtimox. The backbone of secondary prevention lies in the attempt to eradicate *T. cruzi*, to prevent chronic organ damage in the infected host, and to interrupt the epidemiological chain (Rassi, Rassi, and Marin-Neto 2010). However, a clinical trial of benznidazole for CCC demonstrated reductions in parasitemia but no reduction in the progression of cardiac disease over five years (Morillo and others 2015). Advanced medical or surgical prevention strategies aim to reduce morbidity and mortality related to congestive heart failure (see chapter 10 of this volume, Huffman and others 2017), valvular disease, and cardiac arrhythmias (Sosa-Estani, Colantonio, and Segura 2012).

Summary of Costs and Cost-Effectiveness of Interventions

Economic Burden of CD

A recent Markov simulation model estimated the global and regional health and economic burden of CD from the societal perspective to be US$7.2 billion per year and US$188.8 billion for the lifetimes of the whole population of individuals infected (Lee and others 2013). More than 10 percent of these costs were accrued in nonendemic countries. Most of the economic costs arose from lost productivity caused directly by early cardiovascular mortality (Lee and others 2013). Another study addressed the cost of treating patients with CCC who were admitted with decompensated heart failure as compared with other etiologies of acute heart failure. They found that treating CCC was more expensive and mortality was higher in this population at follow-up (Abuhab and others 2013). Finally, a Colombian study estimated that the average lifetime cost of a patient with CCC was US$14,501 (Castillo-Riquelme and others 2008).

Cost-Effectiveness of Interventions for CD

Economic evaluations of CD interventions have focused predominantly on vector control efforts, such as insecticide spraying programs. The economic impact of the Brazilian program was also assessed using both cost-effectiveness and benefit-cost strategies. The program cost US$57 per DALY averted or saved US$25 for every dollar spent on prevention, making it economically very attractive (Moncayo and Silveira 2009).

In Colombia, one study used subnational survey data to assess the incremental cost-effectiveness of spraying versus doing nothing, demonstrating that geographical variation (for example, in higher- versus lower-endemicity regions) had a large effect on the ICER and that resources should be allocated accordingly (Castillo-Riquelme and others 2008). Investigators from Argentina retrospectively assessed the cost-effectiveness of shifting from a vertical (centralized) vector control approach to a community-based, horizontal approach (including a mixed approach incorporating both elements). They found that a mixed approach—a vertical attack phase followed by horizontal surveillance phase led by communities and primary health care centers—would be more cost-effective than either fully horizontal or vertical approaches (Vazquez-Prokopec and others 2009).

Finally, one study of a hypothetical CD vaccine demonstrated that, under a wide variety of assumptions about coverage, effectiveness, and cost, such a vaccine would be very cost-effective and even cost saving (Lee and others 2010). Unfortunately, very little has been written about the cost-effectiveness of secondary or tertiary prevention strategies, which are likely to be relatively more important in the face of decreasing incidence.

CD Conclusions and Recommendations

CD remains an important cause of cardiovascular morbidity and mortality in countries in Latin America and the Caribbean. However, the rapid rollout of effective vector control efforts has led to a dramatic reduction in the incidence of CD and could lead to reductions in CCC in the long term.

We make the following recommendations to endemic countries:

- *Insecticide spraying programs are very cost-effective.* Policy makers in regions where *T. cruzi* is still endemic could embrace a mixed vertical and horizontal approach to vector control. The experiences of Argentina and Brazil can serve as models for other countries.
- *More research is needed on the cost-effectiveness of secondary and tertiary prevention before specific recommendations can be made.* Little is known about the cost-effectiveness of screening individuals and blood bank supplies for evidence of *T. cruzi* or treating CCC with advanced cardiac technologies, such as pacemakers. Prevention of congenital CD may be a high priority area from an equity standpoint. Future research could examine the tradeoffs between ongoing prevention efforts and treatment of existing cases.

CONCLUSIONS

Structural heart diseases are unique because they predominantly affect younger populations and thus contribute substantially to the years of life lost from cardiovascular disease in LMICs. Preventive measures exist for all three conditions, and they are most effective for RHD and CD. Interest is growing in screening programs for structural heart diseases, yet the role of screening is limited in settings where access to advanced medical and surgical care is not available. Most individuals with advanced structural heart disease require surgery, which poses particular challenges in limited-resource settings and provides additional rationale for scaling up cost-effective primary prevention efforts. Our discussion of these three conditions provides decision makers with a framework for public policy that takes into consideration the resources available in various settings. Our recommendations for prevention and management will need to be contextualized to individual settings and integrated into broader cardiovascular disease control policy frameworks.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

1. See the World Heart Federation's website at http://www.world-heart-federation.org/what-we-do/applied-research/rheumatic-heart-disease-demonstration-projects/.
2. See the Chain of Hope at http://www.chainofhope.org/.
3. For example, see the Salaam Centre for Cardiac Surgery at http://salamcentre.emergency.it.

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