Chapter __. Structural Heart Diseases

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Boxes:
Figures:
Maps:
Tables:
Word count: 11,400 words
Graphics requiring permission: Figure 1 from the publishers of "Heart"

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Outline

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 and Chagas disease, are associated with poverty and are preventable. Congenital heart disease, 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, rheumatic heart disease, and Chagas disease. 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

Congenital heart disease (CHD) is the most common 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 colleagues (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 __.1 summarizes the natural history and modified natural history, following surgery or catheter intervention, of common forms of CHD.

Table __.1. Broad Categories of Congenital Heart Disease, Classified according to Natural History

Broad Category	Implications for survival and treatment	Examples*
Critical CHD	Incompatible with survival without specific intervention in newborn period or early infancy	Transposition, 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 atrio-ventricular canal, truncus arteriosus, aorto-pulmonary window, single ventricle physiology, Unobstructed TAPVC, ALCAPA, Severe outflow tract obstructions,
CHD that typically	Diagnosis seldom made in early	Moderate or large ASD, some forms

manifests at an older age	childhood; Intervention required to prevent long- term **sequelae** in adulthood	of coarctation, Some patients with Ebstein's anomaly, relatively less severe forms of aortic and pulmonary valve stenosis, congenitally corrected transposition with intact ventricular septum
Minor CHD	Long-term, symptom free survival can be expected without any specific intervention in most cases	Small L-R shunts (ASD, VSD, PDA) Bicommissural aortic valve

Source: R Krishna Kumar

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

*These examples are not a comprehensive list of conditions; many conditions are not listed. Further, numerous combinations are possible.

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 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,** appear to explain the occurrence of CHD. The recurrence risk in siblings of an affected individual is 1-6 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 to 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 been also 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 __.2 summarizes the risk factors.

Table __.2. Etiology of CHD: Prenatal Exposure to Acquired Factors

Risk Factors	Associations with CHD
Diabetes	Various forms of CHD are linked with maternal gestational and pre-gestational diabetes, including transposition, 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 have a two-fold 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 in two studies; 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 R Krishna Kumar
Note: ASD = Atrial septal defect, CHD = Congenital Heart Disease, NSAID = nonsteroidal anti-inflammatory drugs, PDA = patent ductus arteriosus, SLE = systemic lupus erythematosus, TOF = tetralogy of Fallot, VSD = ventricular septal defect.

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 due to population size, and birth rates are higher in most LMICs (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 has 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 (Stol and others 1999).** Folate deficiency, use of certain medications during pregnancy, maternal diabetes, and phenylketonuria are also modifiable risk factors. Despite the limited 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. Neonatal sepsis or pneumonia are often the first signs of underlying CHD (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 (Zuhkle 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 scarce 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 initiation of screening prior to 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 logistic 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. 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). However, pulse oximetry is very specific but not very sensitive. 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.

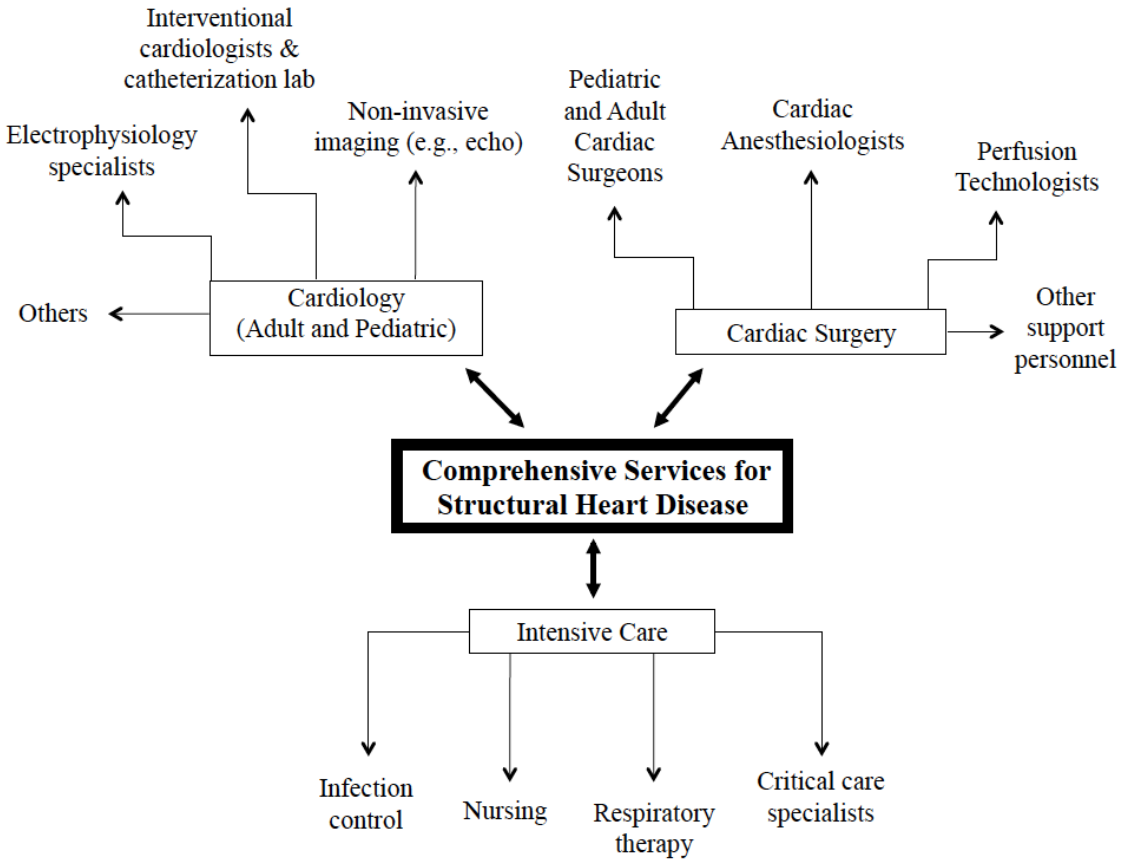
Finally, while routine screening echocardiograms for all newborns is impractical, the use of echocardiography has value in cases where pulse oximetry or clinical examination suggests a higher than usual probability of CHD. Unfortunately, the barriers to widespread availability of echocardiography include 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 2006).

Screening of School Children. Cardiac auscultation is likely to be the most practical strategy for screening school children, since the utility of pulse oximetry in this group is very limited. CHD screening can potentially be integrated with screening for rheumatic heart disease, undernutrition, obesity, and hypertension (Thakur and others 1997, Indian Council of Medical Research 2014**).** Children who are underweight and those with limited physical capacity need to be re-evaluated, 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 __.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 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 prior to 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.

Figure __.1. Organization of Resources Needed To Provide Surgical Care for Structural Heart Diseases



Source: Kumar and Shrivastva 2008

Depending on the type of defect, surgical procedures are designed to either restore normal anatomy and/or physiology or palliate by improving physiology. The latter is more realistic for severe defects that lead to single ventricle physiology. The majority of CHD 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 (Zuhlke, Mrabel, and Marijon 2013).

Several new pediatric heart programs have been established in LMICs, such as 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 (Zuhlke, MIrabel, and Marijon 2013).

Early initiation of treatment of 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 semi-structured interviews, Raj and colleagues (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 (IQR: 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 re-use 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 **2013**).

Cost-Effectiveness of CHD Screening

Most cost-effectiveness analyses of CHD have been conducted in HICs and 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, but the cost-effectiveness data from LMICs are sparse. Given the poor sensitivity and positive predictive valve 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 were 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 co-pays.

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). .

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 due to declining mortality from infectious diseases. Unfortunately, routine screening for CHD prior to 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 for women during early pregnancy:

- **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. 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.

- **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

Rheumatic heart disease (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 five and 15 years. This immune response manifests as acute rheumatic fever (ARF), and severe and recurrent episodes of 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 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 (Silwa 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 preventative treatment, as 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

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, Pacific Islands, and Sub-Saharan Africa**;** many indigenous communities in Asia and Pacific show a high prevalence of RF and RHD risk factors (Carapetis and others 2005; Omurzakova and others 2009). The burden of RHD in terms of prevalence is an active topic in the literature (Zuhlke and Steer 2013). Studies using echocardiography-based methods of measuring prevalence in schoolchildren have demonstrated a 10-fold higher prevalence of valvular abnormalities, compared to prevalence reported using clinical diagnostic methods (Marijon and others 2007). Little is known about the natural history of these asymptomatic cases, compared to the smaller number of symptomatic cases that have **traditionally** been reported (Zuhlke 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 prior to 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 to account for the empirical observation that, at most, 3-5 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 over 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 increasing prevalence and an increasing case load on health systems in LMICs.

Interventions, Platforms, and Policies

RHD Interventions

Primary prevention. Table __.3 summarizes the key points of intervention in the natural history of ARF/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, Asmera, and Parry 2006). Although most of the effectiveness data on primary prevention are older and of lower quality, penicillin is widely regard as the mainstay of prevention and remains in all major clinical guidelines (Marijon and others 2012).

Table __.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 RF/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 RF	80 percent relative risk reduction	Most trials conducted in 1950s-60s in young American males
Secondary prevention of ARF/RHD with benzathine penicillin G	Prevent recurrent episodes of RF and recurrent and progressive heart valve damage	55 percent relative risk reduction (penicillin vs. control); 87-98 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	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

		surgical technique	but generally requires surgical capacity as a backup

Source: Authors
Note: LMICs – low- and middle-income countries; RHD = rheumatic heart disease.

Secondary prevention. Early studies of individuals with a documented history of RF demonstrated that regular secondary preventative therapy with penicillin—especially injectable benzathine penicillin—could reduce the risk of recurrent RF 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 RF 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 RF recurrences averted and reductions in incident RHD (Manyemba and Mayosi 2002).

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 use 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 50-75 percent of ARF cases may have no history of symptomatic pharyngitis.
- Adherence to a regimen of three- to 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 (Zuhlke 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 __.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, that is, 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 than 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 has not been included in standard guidelines and protocols for child health, such as the Integrated Management of Childhood Illness (IMCI) program. This omission is partly due to the fact that most child health programs focus on those under age five years, and streptococcal sore throat and ARF are uncommon in this group. Accordingly, while 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)s, many research groups attempted to develop active case finding programs to increase secondary prevention using echocardiography in community and school settings (http://www.world-heart-federation.org/what-we-do/applied-research/rheumatic-heart-disease-demonstration-projects/). This approach was adopted by the Stop RHD-ASAP Programme at the University of Cape Town (Robertson, Volmink, and Mayosi 2006) and similar programs in the South Pacific (Lawrence and others 2013). Controversy remains about the long-term impact and cost-effectiveness of these programs, as the natural history of cases detected by echocardiogram—and the effectiveness of secondary prophylaxis in this group—is unknown (Zuhlke 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 beyond South Africa (Zuhlke, Mirabel, and Marijon 2013). Three models of initiatives have helped to ameliorate this situation:

- Some well-selected cases are transferred for surgery on a philanthropic basis in 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 (for example, http://www.chaine-espoir.be/).
- Using South-South collaboration, patients are referred to high-volume regional or continental centers, such as in India or Sudan (see http://salamcentre.emergency.it). 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 the benefit of diagnosis or advocacy on their behalf.
- Lower-income countries start to build surgical platforms in their own countries (Binagwaho and others 2013),[68] 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/RHD for LMICs (**WHO 2004)** recommended a package of several types of activities within an integrated RHD program (table __.4). The evidence for these public health initiatives largely comes 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/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).**

Table __.4. Components of an Integrated Program on RF/RHD Prevention and Control

Component activity	Elements	Comments
Planning phase	Establishment of a national	Program should be

	advisory committee; assessment of disease burden; stepwise implementation, monitoring and evaluation	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 (resource-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 200**1**.

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 direct as well as indirect losses in productivity due to chronic disability. Only one study of the economic impact of RHD in a 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 colleagues gathered primary cost data as part of a clinical cost-effectiveness analysis of primary prevention strategies in South Africa (Irlam and others 2013). Finally, in 2015 Watkins and colleagues re-analyzed data from Cuba and found that this combined primary and secondary prevention program cost approximately US$0.07 per year per at-risk child ages 5-14 years.

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 colleagues (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 multi-country 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 acute 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 secondary prevention, compared to other primary and secondary prevention strategies (Manji and others 2013), yet these studies rely on natural history assumptions that have not been borne out by long-term follow-up of echocardiography screening studies (Zuhlke and Mayosi 2013).

Comparative Cost-Effectiveness of RHD Interventions

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

- Watkins and colleagues demonstrated that a comprehensive approach to ARF/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 such high health system costs (Watkins and others 2015).

- Soudarssanane and colleagues (2007) compared primary and secondary prevention and surgery as isolated interventions, measuring benefits in terms of 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). They 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 to secondary prevention. This study extrapolated cost data from the early 1990s and, compared to more recent work, used fairly crude assumptions in the model (Irlam and others 2013).
- Watkins and colleagues updated this analysis using contemporary data on disease epidemiology and costs as well as a lifetime horizon model (Watkins, Lubinga, and Babigumira 2015). They found that both primary and secondary prevention were very cost-effective across a variety of endemic settings, with ICERs less than per-capita GDP of LMICs in Sub-Saharan **Africa.I**n contrast, the decision to scale up surgery—either by increasing case finding and referral to existing facilities in country, or by building a surgical platform—was very context-specific and less likely to be cost-effective in **low-income countries**.

However, building cardiac surgery capacity in low-resource settings might realize economies of scope and scale and educational output in terms of 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.

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 priority and integrated into existing child health interventions. The successful control of ARF/RHD in several Latin American countries was predicated on combining primary and secondary prevention within existing care delivery programs. Such programs are likely 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

Chagas disease (CD) is caused by infection with the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*), and runs through an acute and chronic phase. Diagnosis in the acute phase is rare since most patients are asymptomatic or experience a non-specific 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) as well as 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 1–3 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 non-sustained ventricular tachycardia (Rassi, Rassi, and Rassi 2007; Rassi, Rassi, and Marin-Neto 2009). 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 **9000**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 16–18 million in the 1990s to 8–10 million—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 non-endemic regions, including Australia, Europe, Japan, and the United States (Schmunis 2007). Transmission risk in HICs occurs mostly through the non-vector 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
- Re-spraying of houses with residual infestation
- Subsequent community surveillance.

The classic example is the Brazilian experience during the 1970s-80s, which resulted in a 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 prior to 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 11 of this volume), 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 per lifetime for the whole population of individuals infected **(Lee and others 2013)**. More than 10 percent of these costs were accrued in non-endemic 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 and 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 predominately 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 vs. doing nothing, demonstrating that geographical variation (for example, in higher versus lower endemicity regions) had a large effect on the ICER and should be allocated, where resources permit (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 (Vasquez-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.

Conclusions and Recommendations

Chagas disease remains an important cause of cardiovascular morbidity and mortality in countries in Latin America and the Caribbean. However, the rapid roll out of effective vector control efforts has led to a dramatic reduction in the incidence of CD and will hopefully 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 predominately affect younger populations and thus contribute substantially to the years of life lost from cardiovascular disease in LMICs. Preventative 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 there is not access to advanced medical and surgical care. 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.

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