An important component of the burden of cardiovascular disease in low- and middle-income countries may be attributed to the neglected tropical diseases.

There is a growing awareness of the importance of chronic non-communicable diseases (CNCDs) in the world’s low- and middle-income countries (LMICs). Beginning in the 1990s, Murray and Lopez predicted a doubling of death rates due to cardiovascular disease in developing countries by 2020 [1], while a substantial rise was also predicted by Leeder et al. [2]. Based on World Health Organization (WHO) predictions, 75% of the burden of cardiovascular disease is found in LMICs [3]. Alarming increases have also been noted for other CNCDs in LMICs including cancer, chronic respiratory diseases, and diabetes [4]. In September 2011, a report by the World Economic Forum and the Harvard School of Public Health estimated the global economic burden of CNCDs over the next two decades to be US$47 trillion [5]. During this same month, the United Nations General Assembly held a high-level meeting to discuss prevention and control of CNCDs, including cardiovascular diseases, in LMICs [6]. These initiatives have focused on preventable risk factors attributable to lifestyle changes such as tobacco and alcohol use, prolonged unhealthy nutrition, and physical inactivity, which currently account for a high proportion of cardiovascular deaths in North America and Europe [4–6].

While there is no question that obesity, tobacco, and alcohol represent major underlying conditions responsible for the rise of cardiovascular and other CNCDs in LMICs, they do not provide a complete picture. In March of 2011, Partners in Health and Harvard Medical School sponsored a conference entitled “The Long Tail of Global Health Equity: Tackling the Endemic Non-Communicable Diseases of the Bottom Billion” to examine in more detail some of the neglected causes of CNCDs, particularly those that are unique to the world’s poorest people in LMICs. The conference highlighted important risk factors apart from the lifestyle changes linked to CNCDs in high-income countries [7]. Specifically with respect to neglected populations, an important component of cardiovascular disease may be attributable to neglected tropical diseases (NTDs) and other infections of poverty. For example, the Heart of Soweto Study from South Africa identified rheumatic heart disease, tuberculosis, and HIV as significant contributors to heart disease and more common than coronary artery disease. Even in the urbanized region of Soweto where there is a high prevalence of vascular risk factors, non-ischemic etiologies are still the dominant cause of heart failure [8,9].

On a global level, the contribution of infections of poverty to heart disease can be seen in analyzing the Global Burden of Disease estimates from the WHO. According to this data, approximately 8.8% of the disability-adjusted life years (DALYs) of LMICs may be attributable to cardiovascular disease [3]. Almost one-half of this cardiovascular disease burden is attributable to ischemic heart disease, more than one-third to cerebrovascular disease, and the remainder to hypertensive and inflammatory causes, as well as rheumatic heart disease (Figure 1). A detailed analysis of these conditions suggests that NTDs and other neglected infectious may account for a significant component of each of these cardiovascular disease categories (Table 1).

Protozoan NTDs: American and African Trypanosomiasis

Approximately 10 million people are infected with Trypanosoma cruzi, the etiologic agent of Chagas disease (American trypanosomiasis), of whom up to 30% will develop Chagasic cardiomyopathy associated with heart failure, arrhythmias, and mural thrombi causing pulmonary and systemic emboli and sudden death [10–14]. Chronic heart failure is thought to be due to the persistence of trypanosome amastigotes in the heart, leading to a cascade of tissue destruction, myocarditis, fibrosis, and ultimately ventricular dilation [12]. Arrhythmias are similarly caused by fibrosis. The arrhythmias then predispose to various forms of emboli, and Chagas disease has been linked to ischemia and cerebrovascular disease and even stroke [13,14]. Thus, roughly 2–3 million people at any given time may be affected by Chagas cardiomyopathy, which can present either as ischemic or inflammatory heart disease or with mixed features of both [12–14]. While 99% of the DALYs associated with Chagas disease have been
traditionally attributed to LMICs in the Americas, the “globalization” of Chagas disease from emigration is now recognized as a factor in a previously hidden burden of heart disease in the United States and Europe, especially Spain [15]. Globally, Chagas disease, therefore, accounts for a significant burden of ischemic and inflammatory heart disease in LMICs of the Americas and now accounts for an as yet undefined burden in some high-income countries as well. Similarly, human African trypanosomiasis (HAT) can be associated with myocarditis and pericarditis, especially in the acute stages of the illness when the trypanastigote stages of the parasite spread through the blood and lymphatics to cause endarteritis [16]. On electrocardiography repolarization changes, prolonged QT intervals and low voltage can be seen in infected individuals [17]. About 50,000 to 70,000 people in sub-Saharan Africa are thought to be infected with *Trypanosoma brucei*, with an annual incidence of approximately 17,000, and of infected patients 70% develop the above mentioned electrocardiographic changes [17,18].

**Helminthic NTDs:**

**Endomyocardial Fibrosis, Schistosomiasis, and Hookworm Infection**

Endomyocardial fibrosis (EMF) causing restrictive cardiomyopathy is most prevalent in tropical and subtropical regions in the world. In endemic areas of sub-Saharan Africa, the prevalence of EMF reaches close to 20% and affects mostly children and young adults [19,20]. EMF is currently the fourth leading cause of heart disease in Nigeria, Africa’s most populous country [21,22]. EMF is also associated with pericarditis, arrhythmias, and mural thrombi [22,23]. The etiology of tropical EMF remains unclear; however, a number of factors and helminthic parasites have been implicated in its pathogenesis, particularly because its occurrence has been linked to eosinophilia and hypereosinophilia [22,24]. For that reason, endemic

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**Table 1. Estimated Prevalence of Cardiovascular Disease Caused by Neglected Tropical Diseases and Neglected Infections of Poverty.**

<table>
<thead>
<tr>
<th>NTD</th>
<th>Type of Cardiovascular Disease*</th>
<th>Estimated Number of People with the Infection</th>
<th>Number of Cases of Heart Disease or Related Conditions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chagas disease</td>
<td>Ischemic, cerebrovascular, and inflammatory</td>
<td>10 million</td>
<td>2–3 million</td>
<td>[10–14]</td>
</tr>
<tr>
<td>HAT</td>
<td>Inflammatory</td>
<td>50,000–70,000 in sub-Saharan Africa</td>
<td>Not determined</td>
<td>[16–18]</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Inflammatory</td>
<td>Up to 77% seroprevalence worldwide</td>
<td>19% of AIDS cardiomyopathy associated with acute myocarditis</td>
<td>[50,67,68]</td>
</tr>
<tr>
<td>EMF</td>
<td>Inflammatory</td>
<td>12 million</td>
<td>All</td>
<td>[23,58]</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Inflammatory (cardiomyopathy)</td>
<td>200 million</td>
<td>&gt;270,000 with pulmonary hypertension</td>
<td>[28–34]</td>
</tr>
<tr>
<td>Hookworm</td>
<td>Inflammatory (CHF)</td>
<td>600 million</td>
<td>Not determined</td>
<td>[35–37,69]</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Inflammatory</td>
<td>12 million</td>
<td>Untreated, 10% develop late cardiovascular complications</td>
<td>[40,41,70]</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Inflammatory</td>
<td>2 billion (&gt;10 million infected with HIV)</td>
<td>1%–2% of people with pulmonary TB develop TB pericarditis</td>
<td>[46,48,71]</td>
</tr>
<tr>
<td>HIV</td>
<td>Inflammatory (pericarditis, cardiomyopathy)</td>
<td>34 million people worldwide with HIV and AIDS</td>
<td>Pericarditis: 19%–32% of asymptomatic people with AIDS not on HAART; Cardiomyopathy: 15%–57% of symptomatic and asymptomatic people with AIDS not on HAART</td>
<td>[49,50]</td>
</tr>
<tr>
<td>Dengue</td>
<td>Inflammatory</td>
<td>50–100 million cases annually</td>
<td>Myocardial dysfunction in 6.7% with DF, 13.8% with DHF, 36% with DSS</td>
<td>[54–56,72,73]</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>Ischemic, cerebrovascular, rheumatic</td>
<td>RF: Up to 206/100,000 in developing world</td>
<td>RHD: Up to 18.6/100,000 in developing world</td>
<td>[51,52,74]</td>
</tr>
</tbody>
</table>

*Based on WHO Global Burden of Disease categories.

NTD, neglected tropical disease; HAT, human African trypanosomiasis; AIDS, acquired immune deficiency syndrome; EMF, endomyocardial fibrosis; CHF, congestive heart failure; HIV, human immunodeficiency virus; TB, tuberculosis; HAART, highly active antiretroviral therapy; DF, dengue fever; DHF, dengue hemorrhagic fever without shock; DSS, dengue shock syndrome; RF, rheumatic fever; RHD, rheumatic heart disease.

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filarial infections such as those caused by
Loa loa and Ochocerca volvulus are among the
leading candidate infections linked to
this condition [22,25-27]. Two other
helminths, Schistosoma mansoni and Schisto-
sona japonicum, cause chronic hepatoportal
schistosomiasis, an important cause of
pulmonary hypertension and cor pulmo-
nale. These pathologies occur in response
to parasite egg deposition, hepatoportal
fibrosis, and portal hypertension [28-31].
Lapa et al. calculate that an estimated 200
million people worldwide are infected with
any Schistosoma species, of whom 4%-8%
develop hepatosplenic disease, and greater
than 270,000 will go on to develop
pulmonary artery hypertension [32].
However, more recently, King et al.
suggest that previous estimates have been
underestimating the true impact, and the
prevalence of schistosomiasis-related dis-
ease is closer to 400-600 million world-
wide [33]. Based on even the most
conservative estimates, schistosomiasis
may rank among the most prevalent
causes of pulmonary hypertension world-
wide [32,34]. Finally, among helminths
causin cardiovascular disease, hookworm
infection is a leading cause of iron
deficiency anemia in LMICs [35]. Recent
systematic reviews confirm strong links
between hookworm infection and anemia
among children and both pregnant and
non-pregnant adults [36,37]. In Africa and
Brazil, hookworm and S. mansoni schisto-
somiasis were shown to be synergistic [38].
Severe anemia is an important co-factor in
congestive heart failure, although the
contribution of hookworm disease and
anemia to this condition is unknown.

Bacterial and Viral NTDs and
Neglected Bacterial Infections

In their first ever report on NTDs in
2010, the WHO classified the endemic
treponematoses, including Treponema palli-
dum (the cause of syphilis), as NTDs [39].
Late cardiovascular complications of syphi-
ilis, affecting 10% of untreated cases, cause
obliterative endarteritis leading to syllhi-
litie aortitis. The complications of syllhi-
litie aortitis are coronary artery disease,
valvular disease, and left ventricular vol-
ume overload hypertrophy [40]. A recent
study in India assessing the prevalence of
syphilitic aortitis in non-atherosclerotic
aortic disease found 23% of aortic disease
to be due to syphilis [41]. Tertiary syphilis
can also, less commonly, cause gummato-
tous myocarditis [42]. Of note, however,
cardiovascular syphilis is considered a rare
disease in developed countries [43]. A
more ubiquitous bacteria, Mycobacterium
tuberculosis, leads to another cardiac mani-
festation, tuberculous pericarditis. Among
patients with pulmonary tuberculosis, 1%
to 2% develop tuberculous pericarditis.
The various manifestations can include
myopericarditis, pericardial constriction,
pericardial effusion, and effusive-constric-
tive pericarditis [31]. In sub-Saharan
Africa, 70% to 90% of large pericardial
effusions and 10% of cases of congestive
heart failure are caused by M. tuberculosis
[31,44,45]. While the vast majority of
cases of tuberculosis occur in developing
countries, it is also seen in immigrant
populations of developed countries, and
thus the prevalence of tuberculous peri-
carditis reflects this distribution [46,47].
The disease is frequently diagnosed in
HIV-positive patients, and when it is, it
carries a mortality rate of 40% in 6
months compared to 17% in those without
co-morbid HIV infection [48]. This form
of pericarditis is associated with significant
morbidty and mortality due to the
effusions and constriction that occur
despite appropriate medical therapy [48].
In the absence of M. tuberculosis, untreated
HIV can still cause periocarditis as well as
other forms of cardiovascular disease,
including pulmonary hypertension and
cardiomyopathy [49]. In Africa, toxoplas-
mosis and cryptococcosis are also impor-
tant opportunistic infections associated
with cardiomyopathy [50]. Finally, 80%
of rheumatic heart disease associated with
group A streptococcal infection occurs in
LMICs [51]. The WHO data depicted in
Figure 2 demonstrate the skewed burden
weighted toward LMICs of the world,
specifically in the Middle East and Asia,
where substantially higher disease burdens
due as measured in DALYs) exist [3]. These
projections likely even underestimate the
true burden of disease based on recent
evidence [51]. The weighted burden
among LMICs is a relatively new phe-
nomenon. Prior to the 1970s, rheumatic
fever was an important cause of morbidity
in developed countries; however, in the
1970s and 1980s, the prevalence of
rheumatic fever began to decrease, while
the rates in developing countries are an
ongoing challenge and contribute signifi-
cantly to the burden of disease [52]. The
inequity between the wealthy and the poor
can be seen even in high-income countries
today where rheumatic heart disease
disproportionately affects people living in
poverty and indigenous populations
[51,53]. Without adequate treatment, the
mitral valve abnormalities characteristic of
rheumatic heart disease predispose pa-
tients to other cardiac pathologies such as
infectious endocarditis [8], thus making
rheumatic heart disease a contributing
factor to both ischemic and cerebrovascu-
lar disease. Among the viral NTDs, most
notably dengue fever has been associated
with systolic and diastolic cardiac impair-
ments [34], as well as myocarditis [35,36].

Policy Recommendations

We lack adequate data to determine the
true extent of human cardiovascular
disease that results from NTDs and other
neglected infections of poverty. It also
remains unclear how much of the world’s
ischemic heart disease and cerebrovascu-
lar disease, which account for most of the
disease burden, may be due to neglected
causes. There is an urgent need to
understand the contribution of neglected
diseases to heart disease in LMICs in order
to design appropriate intervention strate-
gies. This has been highlighted by others
in the field who also acknowledge the
presence of unique risk factors and heart
pathologies in LMICs [8,11,20,31,57,58].

Toward that goal, stepped up measures
for some of the neglected parasitic diseases
might include increased screening for
Chagas disease in the Americas (including
the United states), Europe, and elsewhere
using antibody-based testing now available
[59]. Doppler testing for pulmonary hy-
pertension that results from schistosomiasis
in Africa, and investigations into the
etioloogy of EMP, especially tropical EMP
linked to eosinophilia. Similarly, the extent
to which bacterial infections such as
syphilis, tuberculous pericarditis, and
rheumatic heart disease (RHD) contribute
to cardiovascular disease in LMICs re-
mains unclear and requires improved
diagnostic capabilities and testing. For
RHD in particular, echocardiographic
screening in school-aged populations is
recognized as an important method of
identifying subclinical rheumatic heart
disease in the early stages prior to the
progression to heart failure [53]. Such
diagnostics and testing requires improved
health systems in the developing world.
Bukhman and Kidder have outlined novel
methods of integrating services for RHD
and heart failure into existing health
systems in LMICs [60,61]. This can be
expanded upon and tailored to specific
regions.

There also remains a dearth of ade-
quate control tools, that is, new drugs or
vaccines for the neglected causes of human
cardiovascular disease in LMICs. For
instance, benzimidazole and nifurtimox,
the currently available drugs for treating
Chagas cardiomypathy, require long
treatment courses, and exhibit high levels
of toxicities [62]. Their efficacy in achieving parasitologic cure is also in doubt and complicated by the absence of adequate biomarkers for assessing either progression of disease or clinical outcomes [63,64]. As an alternative intervention, efforts are in progress to develop and test therapeutic vaccines for Chagas disease [64]. Without a clear etiology, interventions for EMF beyond palliative surgeries for restrictive cardiomyopathy will be difficult to develop and test, while for schistosomiasis and hookworm there are needs to greatly expand coverage for annual mass drug administration using currently available anthelminthic drugs, as well as develop new anthelminthic vaccines to prevent anemia and heart disease, and forestall drug resistance [38]. For neglected bacterial infections, there is a need to accelerate new vaccines for tuberculosis [65,66] and RHD [57] now in different stages of development, while the incidence of syphilis-associated heart disease may be reduced through expanded drug coverage.

Finally, as identified by Commerford and Mayosi, when the etiology and control mechanisms are known, research should include identifying social determinants that prevent disease management. Social determinants such as health systems, attitudes, and perceptions of both patients and physicians and socioeconomic factors should all be explored and recognized as important aspects of cardiovascular disease control and variable between ethnic groups [8]. With all the information gathered, the cost of prevention and control can be compared to the burden cost of the various causes of cardiovascular disease in LMICs.

Together, these interventions will address significant neglected causes of cardiovascular disease burden especially prevalent in LMICs. The growing interest in cardiovascular disease in these resource-poor settings is necessary to ensuring the health of the working-age population. Careful analysis reveals the need to look beyond lifestyle risk factors of developed countries and appreciate the nuances of chronic disease in developing countries. In doing so, we will more effectively facilitate the economic advancement of low- and middle-income populations.

Supporting Information

Table S1 List of countries in WHO income-based regions. (DOCX)

References


