

## Linking Tropical Infections to Hypertension: New Comorbid Disease Paradigms in Our Era of “Blue Marble Health”

Peter J. Hotez, MD, PhD

We are beginning to see shifts in our 21st century global health framework. The “grand decade of global health” that heralded the beginning of this new millennium emphasized the obligations of wealthy countries to support poverty-related infectious disease control in the poorest nations.<sup>1,2</sup> Indeed, for the United States, United Kingdom, and other donor nations (often operating through agencies of the United Nations), it was a highly productive period that led to the creation of the US President’s Emergency Plan for AIDS Relief and the President’s Malaria Initiative, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and neglected tropical disease (NTD) programs, in addition to the Bill & Melinda Gates Foundation.<sup>1,2</sup> As a result, millions of people gained access to essential medicines for HIV/AIDS, malaria, tuberculosis, and NTDs.<sup>2</sup> The impact of the decade of global health programs was especially apparent in the poorest, most devastated nations of sub-Saharan Africa and southeast Asia, where tremendous public health gains ensued.<sup>2</sup>

Now, almost 2 decades after the launch of the United Nations Millennium Development Goals for poverty reduction, our studies find that the world has altered significantly in terms of the distribution of its major poverty-related neglected diseases: HIV/AIDS, malaria, tuberculosis, and NTDs.<sup>3,4</sup> As many African and Asian economies have significantly grown, partly as a consequence of the decade of global health’s overseas development aid, the distinction between more developed and less developed economies appears to have blurred. With the exception of those nations devastated by war and conflict, as well as those in postconflict recovery mode, almost all national economies are expanding. And

despite the setback from the 2008 recession, global economic growth appears to be robust, although uneven.<sup>5</sup> The consequence of this shift is that now most of the world’s poverty-related neglected diseases and NTDs paradoxically are mostly found in the largest economies, including the group of 20 nations, Nigeria, and other African nations exhibiting strong economic growth.<sup>3,4</sup> The term “blue marble health” has been used to describe a new phenomenon of the poor left behind in the midst of strong economic growth and expansion.<sup>3,4</sup> Today, the poor living among the wealthy, a group we sometimes refer to as the “poorest of the rich,” bear the greatest burden of the poverty-related neglected diseases.

Blue marble health also finds that the poorest of the rich probably also account for most of the world’s major noncommunicable diseases (NCDs), such as diabetes mellitus and cardiovascular diseases.<sup>6</sup> Therefore, we are living in a new era in which the poor, but especially the poorest of the rich, get hit times 3: (1) the poorest of the rich experience the consequences of being marginalized living in close proximity to wealth; (2) they disproportionately experience poverty-related neglected diseases and NTDs; and (3) they disproportionately experience NCDs.

Not surprisingly, we are now finding new comorbidities arising from the fact that the poor or the poorest of the rich simultaneously experience poverty-related neglected diseases and selected NCDs. For example, in India and elsewhere, those now suffering the most from dengue in terms of severity of illness and even death are the dengue-infected individuals with underlying diabetes mellitus and hypertension.<sup>7</sup> A similar finding has been made in diabetic patients who acquire tuberculosis.<sup>8,9</sup> But we are only at the beginning of uncovering the major links between NTDs and NCDs.

### Malaria and Hypertension

In this issue of the *Journal of the American Heart Association (JAHA)*,<sup>10</sup> Etyang et al, from the Wellcome Trust Research Programme of the Kenya Medical Research Institute, use an innovative study design to uncover a new and unexpected link between a neglected disease and an NCD (namely, a potential association between malaria and hypertension). Specifically, the Wellcome group compared a population living in an area of

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From the Departments of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX (P.J.H.); and Department of Biology, Baylor University, Waco, TX (P.J.H.).

**Correspondence to:** Peter J. Hotez, MD, PhD, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030. E-mail: hotez@bcm.edu

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Kenya (Kilifi), where moderate malaria transmission occurs, with a malaria-free transmission area of Nairobi, Kenya, and Jackson, MS, in the United States, where malaria transmission was interrupted in the middle of the 20th century.<sup>11</sup> Among these 3 populations, they used sickle cell trait as a biomarker for protection against malaria, a concept best first articulated by A.C. Allison working in Uganda and Kenya, who showed in the 1950s that individuals with sickle cell trait “suffer from malaria less often and less severely than those without the trait.”<sup>12</sup> The Kenya Medical Research Institute group found that sickle cell trait was associated with a reduction in systolic blood pressure and lower hypertension prevalence in the Kilifi site, where malaria is endemic, whereas in the 2 nonmalaria endemic areas of Kenya and the United States, respectively, there was no blood pressure or hypertension reduction.<sup>10</sup> Their conclusion is that protection against malaria reduces blood pressure or, conversely, living in a malaria-endemic area with chronic malaria exposure and infection is associated with hypertension.<sup>10</sup>

The link to malaria and hypertension in Kenya is an intriguing possibility, and one that potentially generates several interesting hypotheses. For example, is this a new phenomenon attributable to changes in diet or access to a more westernized diet in Kilifi? Is it the consequence of an older population who now lives longer because of local disease control efforts? What if this study had been conducted decades earlier, would the results have been the same? Or what if the study were repeated in an area of sub-Saharan Africa considered more remote and without any access to modern-style restaurants, disease control efforts, or hope for longer life expectancies? Also, are the reported results related to the blue marble concepts highlighted above

and the consequences of malaria running into emerging hypertension in an area hosting both poverty and economic advances and development?

## Other Infections and Hypertension

The Kenya Medical Research Institute authors identify some potential mechanisms to explain the malaria–high blood pressure links, including malaria-induced chronic inflammation, growth stunting, and anemia or other forms of malnutrition, each with the potential ability to promote hypertension.<sup>10</sup> These are certainly interesting hypotheses to explore, but they are not necessarily limited to malaria and hypertension links. Indeed, malaria is not the first human infectious disease linked to hypertension, and host inflammation and other factors have been identified as potential mechanisms (Table).

## Herpesviruses

A decade ago, a group from Harvard Medical School reported on findings using a mouse model that cytomegalovirus, a common herpesvirus of adults, causes significant increases in arterial blood pressure, possibly operating through proinflammatory cytokines, including interleukin-6 and tumor necrosis factor- $\alpha$ , together with upregulation of renin and increased angiotensin-II production.<sup>13</sup> Furthermore, high cytomegalovirus immunoglobulin G antibody levels are associated with increased mortality among an aging Latino population, and this association may also be linked to interleukin-6 and tumor necrosis factor- $\alpha$  levels.<sup>14</sup> Another herpesvirus, human herpesvirus-8, was noted to be linked to primary pulmonary hypertension,<sup>15</sup> although these results were not confirmed in a different study.<sup>16</sup>

**Table.** Infectious Diseases Linked to Hypertension

Disease	Type of Agent	Proposed or Potential Link or Mechanism	Reference
Dengue	Virus	Increased dengue mortality in patients with underlying hypertension	7
Malaria	Protozoan Parasite	Chronic inflammation Growth stunting Malnutrition	10
Cytomegalovirus infection	Virus	Chronic inflammation (interleukin-6/TNF- $\alpha$ ) Upregulation of renin/angiotensin	13, 14
HHV-8	Virus	Not determined	15, 16
HIV/AIDS	Virus	Chronic inflammation HIV nephropathy Lipodystrophies Microbial translocation	17, 18
Periodontal disease	Bacterial infection	Not determined	19
<i>Chlamydia</i> and <i>Helicobacter</i> infections	Bacterial infection	Chronic inflammation	20

HHV-8 indicates human herpesvirus-8; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

## HIV/AIDS

Adults with HIV/AIDS, especially those receiving antiretroviral therapy, have a high prevalence of hypertension, relative to individuals not infected with HIV.<sup>17</sup> Moreover, HIV-infected hypertensive adults have twice the risk of myocardial infarction compared with uninfected adults.<sup>17</sup> Several mechanisms have been proposed to explain these findings, including the possibility that antiretroviral therapy itself is responsible for the hypertension. However, increasingly, there is a body of evidence suggesting that hypertension might be secondary to the virus infection itself. The potential mechanisms by which HIV/AIDS results in hypertension include chronic inflammation (also associated with elevation in interleukin-6, as well as other mediators); breakdowns in mucosal defenses, resulting in microbial translocation into the systemic circulation; immunological reconstitution secondary to antiretroviral therapy; lipodystrophies that may result from either the virus or antiretroviral therapy, with potential roles for the adipokines, adiponectin, and leptin; neuroendocrine responses; and HIV-associated renal disease.<sup>17,18</sup>

## Bacterial Infections

Chronic bacterial periodontal disease is also linked to hypertension and cardiovascular disease, especially stroke.<sup>19</sup> Specifically, individuals with a relative excess of oral bacterial pathogens had increases in both systolic and diastolic blood pressures and were shown to be at increased risk for hypertension.<sup>19</sup> In this case, systemic inflammation, as measured by increased white blood cell counts and C-reactive protein levels, varies, depending on the study.<sup>19</sup> There are also conflicting accounts of the potential role of *Chlamydia pneumoniae* or *Helicobacter pylori* in producing hypertension, as well as atherosclerosis and metabolic syndrome.<sup>20</sup>

## Concluding Comments

As yet, there is no common or unifying hypothesis linking infection to hypertension. Chronic inflammation is a route often proposed, but the specific mechanisms by which infectious pathogens lead to hypertension are still elusive. However, the most recent evidence that chronic malaria may predispose to hypertension has enormous implications for the world's malaria-endemic areas. This is especially true for sub-Saharan Africa, where NCDs, especially diabetes mellitus and hypertension, are rapidly increasing, particularly as Africa becomes increasingly urbanized and becomes reshaped into large megacities. Therefore, just as dengue is now emerging as an important complication of NCDs in India and elsewhere, the same may turn out to be the case for malaria in Africa.

## Disclosures

Hotez is an inventor on patents for vaccines to prevent or treat neglected tropical diseases, including hookworm infection, schistosomiasis, and Chagas disease.

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