

The burden of cardiovascular disease in the Indian subcontinent

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Received August 17, 2006

Ischaemic heart disease and stroke are among the most common causes of death and disability in the world. The Indian subcontinent (including India, Pakistan, Bangladesh, Sri Lanka, and Nepal) has among the highest rates of cardiovascular disease (CVD) globally. Previous reports have highlighted the high CVD rates among South Asian immigrants living in Western countries, but the enormous CVD burden within the Indian subcontinent itself has been underemphasized. In this review, we discuss the existing data on the prevalence of CVD and its risk factors in the Indian subcontinent. We also review recent evidence indicating that the burden of coronary heart disease in the Indian subcontinent is largely explained on the basis of traditional risk factors, which challenges the common thinking that South Asian ethnicity per se is a strong independent risk factor for coronary heart disease. Finally, we suggest measures to implement in policy, capacity building, and research to address the CVD epidemic in the Indian subcontinent.

“Live sensibly - among a thousand people, only one dies a natural death; the rest succumb to irrational modes of living.” - Maimonides

Ischaemic heart disease and stroke are the two most common causes of death worldwide¹. Over 80 per cent of deaths and 85 per cent of disability from cardiovascular disease (CVD) occur in low- and middle-income countries²⁻⁴. The Indian subcontinent (including India, Pakistan, Bangladesh, Sri Lanka, and Nepal) is home to 20 per cent of the world's population and may be one of the regions with the highest burden of CVD in the world. Although studies have documented that immigrants from the Indian subcontinent (South Asians) living in Western countries have a higher burden of cardiovascular disease than other ethnicities⁵⁻⁷, less attention has

been paid to the enormous burden of CVD in the Indian subcontinent itself. We discuss here (i) the available data on the CVD burden in the Indian subcontinent and the limitations of the data; (ii) the prevalence of CVD risk factors in the Indian subcontinent; (iii) how the high rates of coronary heart disease (CHD) in the Indian subcontinent can be explained by traditional environmental and biological risk factors, offering a challenge to the prevailing wisdom that South Asian ethnicity *per se* is an independent risk factor for CHD; and (iv) steps in policy, capacity building, and research to tackle the CVD epidemic in the Indian subcontinent.

The estimated burden of CVD the Indian subcontinent

The absence of reliable mortality data in the Indian subcontinent has necessitated estimates of the CVD burden based on cross-sectional studies that have been well described previously^{8,9}. In 2003, the prevalence of CHD in India was estimated to be 3-4 per cent in rural areas (two-fold higher compared with 40 yr ago), and 8-10 per cent in urban areas (six-fold higher compared with 40 yr ago), with a total of 29.8 million affected (14.1 million in urban areas, and 15.7 million in rural areas) according to population-based cross-sectional surveys^{9,10}. This estimate is comparable to the figure of 31.8 million affected, derived from extrapolations of the Global Burden of Diseases study^{1,9,10}. However, these numbers are still likely underestimates as they do not account for those with silent myocardial infarction or otherwise asymptomatic CHD. In 1990, there were an estimated 1.17 million deaths from CHD in India, and the number is expected to almost double to 2.03 million by 2010¹¹. In addition to the high rate of CHD mortality in the Indian subcontinent, CHD manifests almost 10 yr earlier on average in this region compared with the rest of the world^{9,12}, resulting in a substantial number of CHD deaths occurring in the working age group. In Western countries where CVD is considered a disease of the aged, 23 per cent of CVD deaths occur below the age of 70; this compares with 52 per cent of CVD deaths occurring among people under 70 yr of age in India^{9,11}. As a result, the Indian subcontinent suffers from a tremendous loss of productive working years due to CVD deaths: an estimated 9.2 million productive years of life were lost in India in 2000, with an expected increase to 17.9 million years in 2030 (almost ten times the projected loss of productive life in the United States)³. The health and economic implications of this staggering rise in early CVD deaths in South Asian countries are profound and warrant prompt attention from governing bodies and policy makers of these countries.

The burden of CVD risk factors in the Indian subcontinent

The huge burden of CVD in the Indian subcontinent is the consequence of the large population and the high prevalence of CVD risk factors. Moreover, the projected increase in deaths and disability from CVD is expected to follow closely an explosion in the prevalence of traditional risk factors. Driving this steep rise in CVD risk factor burden is the rapid increase in the proportion of urban inhabitants (currently at 30% with a projected rise to 43% in 2021)⁸. Urbanization is characterized by a marked increase in the intake of energy-dense foods, a decrease in physical activity, and a heightened level of psychosocial stress, all of which promote the development of dysglycaemia, hypertension, and dyslipidaemia⁴.

Diabetes mellitus: The Indian subcontinent has a higher prevalence of diabetes mellitus than any other region in the world, and 2-3 times the reported prevalence in Western countries¹³. In India alone, an estimated 19.3 million people had diabetes in 1995, and this is expected to almost triple to 57.2 million in 2025¹⁴. The Indian Council of Medical Research (ICMR) estimates that the prevalence of diabetes is 3.8 per cent in rural areas, compared with 11.8 per cent in urban areas⁸. This might be a substantial underestimate, according to some preliminary cross-sectional survey data from Bangalore as part of the ongoing Prospective Urban Rural Epidemiologic (PURE) study (Vaz M, Kurpad A and Yusuf S, unpublished data).

Hypertension: Hypertension is even more prevalent (20-40% among urban and 12-17% among rural adults)¹⁵, and was affecting an estimated 118 million inhabitants in India in 2000; this number is projected to almost double to 214 million in 2025¹⁶. Similarly, the 1990-1994 National Health Survey of Pakistan revealed that one third of the Pakistani population over the age of 45 yr had hypertension¹³.

Chronic kidney disease: Concomitant with the rise in the prevalence of diabetes and hypertension is an increase in the prevalence of chronic kidney disease, also recognized as an independent risk factor for CHD¹⁷. A study from Pakistan reported a prevalence of 15-20 per cent of reduced estimated glomerular filtration rate among people of 40 yr of age or older¹³; data from India suggest a prevalence of chronic kidney disease of 0.8-1.4 per cent in urban areas^{18,19}, although this is likely a significant underestimate given the absence of a kidney disease registry in India and low rates of screening for chronic kidney disease.

Cigarette smoking: In 2002, a national survey of tobacco use reported that the Indian subcontinent, second only to China in both the production and consumption of tobacco products, had an alarming rate of current tobacco use of 56 per cent among Indian men aged 12-60 yr⁸. Reddy and colleagues also recently observed in a survey of sixth and eighth graders attending school in an urban setting that the prevalence of tobacco use (any history of use or current use) was 2-3 times higher among sixth graders compared with eighth graders²⁰, suggesting a concerning new wave of smoking among India's youth that forebodes serious future public health consequences for the Indian subcontinent.

Other forms of tobacco use: In addition to the high prevalence of cigarette smoking, other forms of tobacco use are common in South Asia, including reported prevalences of smoking beedies (a small amount of tobacco wrapped in a temburini leaf) of 5.9 per cent among males, and of smokeless tobacco (chewing tobacco or chewing paan) of 7.3 per cent (5.5% in women and 7.6% in men)²¹. Little data have existed regarding the association between the use of other forms of tobacco and the risk of CVD; however, a recent analysis of data from the INTERHEART case-control study of risk factors for acute myocardial infarction (MI)¹² has documented that there is an increased risk of myocardial infarction associated with all forms of smoked and smokeless tobacco²¹. Smoking beedies was associated with an age- and sex- adjusted odds ratio (OR) of 2.89 for acute

myocardial infarction [95% confidence interval (CI) 2.11-3.96] compared to non-use, a risk that was comparable to the risk of current cigarette smoking (OR 2.95, 95% CI 2.77-3.14). In addition, there was a graded increase in risk associated with the number of beedies smoked per day, a finding also demonstrated for cigarette smoking. The risk of having an acute myocardial infarction associated with the use of chewing tobacco was also increased (OR 2.23, 95% CI 1.41-3.52). Furthermore, the INTERHEART investigators found that 40 per cent of people who used smokeless tobacco also smoked cigarettes, and in these individuals there was a compounded risk of acute myocardial infarction associated with the use of both chewing tobacco and smoking cigarettes (OR 4.09, 95% CI 2.98-5.61 compared with the non-use of tobacco products). Although all of these reported odds ratios are for the entire INTERHEART cohort, analysis in only the South Asian countries revealed the same degree of risk associated with all forms of tobacco use. Therefore, use of tobacco in forms other than cigarette smoking (*e.g.*, beedies) is both common and important contributors to the CHD burden in South Asia.

Dyslipidaemia: The ICMR surveillance project reported a prevalence of dyslipidaemia (defined as a ratio of total to HDL cholesterol >4.5) of 37.5 per cent among adults aged 15-64 yr, with an even higher prevalence of dyslipidaemia (62%) among young male industrial workers⁸. The INTERHEART investigators reported that the prevalence of dyslipidaemia (abnormal apolipoprotein ApoB/ApoA1 ratio) among controls without acute myocardial infarction was higher among study participants living in the five South Asian countries (45%) compared with participants from the other 47 countries represented in the study (35%) (unpublished data). As in the overall INTERHEART population, abnormal ApoB/ApoA1 ratio was the single largest contributor to the population attributable risk for acute myocardial infarction in South Asian countries. The impact of dyslipidaemia on the burden of CHD has been otherwise

understudied at a population level in native South Asians, despite its large contribution to CHD in other world populations.

Alcohol consumption: Mild to moderate alcohol consumption has been associated with lower rates of CVD events in multiple Western-based observational studies²²⁻²⁴. However, Joshi and colleagues in the INTERHEART South Asia study reported that consumption of alcohol was not associated with myocardial infarction in any of the South Asian countries (OR for acute myocardial infarction associated with alcohol intake 1.06, 95 per cent CI 0.85-1.30 for South Asia, compared with OR 0.79, 95 per cent CI 0.74-0.85 for the rest of the world) (unpublished data). The authors postulated that this may be due to differences in the typical pattern of alcohol consumption among inhabitants of the Indian subcontinent (consumption of relatively large quantities of alcohol on an irregular basis, *i.e.*, binge drinking) compared with other world populations (consumption of relatively small quantities of alcohol on a regular basis). However, this observation requires further corroboration and more careful study of the association between patterns of alcohol intake and CVD risk in the Indian subcontinent.

Fruit and vegetable intake: A review of 250 observational studies estimated that increased consumption of fruits and vegetables is associated with a 16 per cent lower risk of cardiovascular deaths²⁵, a result that is consistent with the overall results of the INTERHEART study¹². It is commonly believed that inhabitants of South Asia consume large quantities of fruits and vegetables, in part because of the high prevalence of vegetarianism in South Asia. However, careful analysis of the INTERHEART data revealed that South Asians actually had a lower prevalence of daily fruit and vegetable intake (26.5% among control arm patients who did not have an acute myocardial infarction) compared with the rest of the world (45.2% among control arm patients from the 47 non-South-Asian countries) (unpublished data). Although vegetarian, the meals of many

South Asians consist of large quantities of carbohydrates such as rice and bread (which predisposes to atherogenic dyslipidaemia including hypertriglyceridaemia and low HDL cholesterol), ghee and fried foods (high in saturated fat), and processed foods (many of which are high in trans-fatty acids). Moreover, the vegetables that are consumed are often overcooked (a process which has been shown to diminish their content of potentially protective micronutrients compared with raw or properly cooked vegetables²⁶).

Physical activity: A recent hospital-based case-control study from two urban centers in India suggested that daily moderate intensity physical activity (*e.g.*, the equivalent of briskly walking 35-40 min per day) is associated with a 55 per cent lower risk for CHD²⁷. In the INTERHEART study, the prevalence of leisure time physical activity was substantially lower among South Asians (6.1% of control arm patients) compared with the rest of the world (21.6%) (unpublished data). Cultural norms, such as the perceived impropriety of women's engaging in leisure time physical activity in certain Muslim communities (unpublished data) may be in part responsible for these low rates of physical activity.

Can the greater burden of CVD in the Indian subcontinent compared to the rest of the world be explained by traditional CVD risk factors?

In the past decade, studies have reported a higher burden of CVD among South Asians compared with other populations, despite the South Asian populations in these studies having a similar or smaller burden of traditional CVD risk factors compared with other ethnicities^{5,7}. This has led to experts suggesting that South Asian ethnicity *per se* is a risk factor for CVD that is independent of traditional risk factors. However, these prior studies were characterized by several important limitations: (i) few studies focused on the burden of CVD among South Asians living in their own countries; (ii) there were relatively few clinical events to reliably

compare the contributions of various risk factors on the presence of CVD; (iii) data were collected on the presence or absence of certain risk factors, and not the intensity or pattern of exposure to these risk factors and their relationship to CVD; (iv) data on dietary patterns, physical activity, abdominal obesity, alcohol intake, and psychosocial factors were often not collected; and (v) data on dyslipidaemia included only crude lipid measures such as total cholesterol instead of apolipoproteins (ApoA1 and ApoB).

Recently, the INTERHEART case-control study reported that nine risk factors [blood apolipoproteins (ratio of apoB to ApoA1), smoking (number of cigarettes smoked per day), self-reported hypertension, self-reported diabetes mellitus, abdominal obesity (assessed by waist-to-hip ratio), psychosocial stressors, and three “protective” factors (leisure-time physical activity, intake of fruits and vegetables, and alcohol consumption)] was associated with over 90 per cent of the population attributable risk for myocardial infarction in the world (and as high as 94% in women)¹². The impact of these risk factors in different populations around the world were equally robust and similar, including in the Indian subcontinent. This suggests that these risk factors account for the majority of MI in India, as well as globally.

The INTERHEART investigators have more recently completed a detailed analysis focusing on the CVD risk profile among the 1732 cases and 2204 age-matched controls from the five South Asian countries (unpublished data). Compared with study participants from the other 47 countries in the world, South Asians had a lower mean age for first acute myocardial infarction (53 vs 58.8 yr of age). However, there were important differences between the risk factor profiles of South Asians compared with non-South Asians. South Asians had a higher burden of metabolic risk factors (ApoB/ApoA1 ratio, diabetes mellitus, and waist-to-hip ratio) and a higher prevalence of use of smokeless tobacco, particularly in rural settings and among women, compared with other

populations in INTERHEART. In addition, South Asians had lower rates of protective factors (physical activity, daily intake of fruits and vegetables, and regular but moderated alcohol consumption). When age strata were compared between South Asians and other ethnicities, South Asians actually had higher levels of risk factors than non-South Asians for all age strata under 60 yr. However, after adjusting for all nine risk factors within each age stratum, the risk of acute myocardial infarction was similar in South Asians compared with the risk in participants from the rest of the world. These data challenge the prevailing wisdom that South Asian ethnicity by itself is a risk factor for acute myocardial infarction. Instead, it suggests that the higher levels of risk factors in South Asians may be primarily responsible for their higher rates of CHD. These data also suggest that aggressive screening for and modification of traditional risk factors in South Asians at an early age could substantially reduce the high rates of early-onset CHD in this population.

What steps should be taken to address the enormous CVD burden in the Indian subcontinent?

Steps in policy: Recognition that the vast majority of the CVD burden in the Indian subcontinent is due to environmental factors has led to the understanding that the greatest impact on the CVD burden in the Indian subcontinent will come from implementing societal changes through policy interventions^{8,28}. However, the Indian subcontinent is home to a heterogeneous population for which a “one size fits all” policy approach to addressing the CVD burden is likely to be insufficient. Different manifestations of CVD (reflecting different stages of the epidemiologic transition of CVD⁴ can be observed not only between urban and rural populations, but also in between poor and wealthy households that live side by side in the same neighbourhood, making even regional CVD prevention programmes (let alone national programmes) a challenge to implement effectively. Currently, public health programmes and

health systems in South Asia have been designed to address primarily communicable diseases and conditions affecting maternal and child health⁸; prevention and control of chronic diseases (which have been incorrectly perceived as affecting only the wealthy population that seeks health care from the private sector) have not been integrated adequately by these public programmes.

Tobacco cessation: For the prevention of chronic diseases (in particular CVD), the highest priority for the Indian subcontinent is tobacco cessation, for which notable strides have already been achieved. The Indian government's enactment of the Tobacco Control Act in 2003 has mandated bans on smoking in public places, on tobacco advertising and tobacco use in the film industry, and on tobacco sales to minors or near educational institutions. India has also adopted the World Health Organization's Framework Convention on Tobacco Control. However, lack of a national regulatory authority for tobacco control hinders enforcement of these policies⁸. Greater concentration of tobacco cessation efforts must be applied to those groups in whom tobacco use rate trends are particularly disturbing, including the youth²⁰, and rural populations in whom the use of smokeless tobacco and use of tobacco among women are highly prevalent²¹. Moreover, innovative means are required to address the even greater challenge of controlling the use of other forms of tobacco (beedies, chewing tobacco, and paan). Finally, in addition to the challenges in India, similar tobacco cessation policies and efforts in Pakistan, Nepal, Sri Lanka, and Bangladesh are lacking.

Lifestyle modification: Structured programmes to promote healthy dietary patterns and physical activity must be developed to combat the deleterious effects of urbanization. Policy efforts are needed to (i) reduce carbohydrate intake on a population basis to lower rates of abdominal obesity and atherogenic dyslipidaemia (high triglycerides and low HDL cholesterol), (ii) reduce the sodium content of packaged foods (e.g., jarred pickle or snacks) to lower the prevalence of hypertension, and (iii) increase

regular consumption of fresh fruits and vegetables to lower CHD risk. In addition, cultural norms that hinder the adoption of healthy lifestyles should be appreciated so that novel approaches to encourage healthy lifestyles can be developed and implemented in a culturally sensitive manner (e.g., engaging and educating the leaders of the community to encourage leisure-time physical activity among urban men and women).

Steps in capacity building: Capacity building of the research infrastructure in all aspects, including clinical research training of physicians and health care workers, development of clinical trial and epidemiology networks, and formation of ethics boards, is essential to enable countries in the Indian subcontinent to conduct high-quality research on the scope, determinants, and control of the CVD epidemic. The absence of reliable mortality data has necessitated the use of estimates of the CVD burden, which are often inadequate to guide policy makers^{8,9}. National surveillance programmes to determine the causes of death and disease and the prevalence of risk factors must be established to document accurately the scope, trends, and regional variations of the problem. The knowledge and awareness of the CVD epidemic among the lay public (adults and children), policy makers, and health care providers must be assessed to guide the effective development and implementation of policy interventions.

Steps in research: Several steps can be taken to bolster the research agenda to help characterize and treat CVD and its underlying risk factors in South Asia.

(i) Reliable statistics of rates of CVD and its underlying risk factors are required to inform the development of sound policy changes to promote cardiovascular health. This can be achieved through the conduct of high-quality, large cohort studies that sample participants from both urban and rural settings. For example, the ongoing Prospective Urban and Rural Epidemiologic (PURE) study is a prospective cohort study that aims to understand the

determinants and rates of several chronic diseases in over 135,000 people from about 15 countries worldwide, including 30,000 from India. Studies such as PURE will help quantify the impact of urbanization on risk factors for chronic diseases, and shape policy efforts to address risk factor profiles that are unique to urban versus rural areas. Reliable statistics can also be obtained by establishing registries that are linked to already ongoing clinical trials. For example, the CREATE-ECLA trial (testing the use of reviparin and glucose-insulin-potassium therapy using a 2×2 factorial design) enrolled 20,201 acute myocardial infarction patients from 274 sites around the world^{29,30}. Of these patients, 8,060 were enrolled from 71 sites in the Indian subcontinent (67 from India and 4 from Pakistan). During the course of the CREATE trial, the investigators established the CREATE registry that included patients with acute coronary syndromes. The CREATE registry, however, contains a wealth of data on over 20,000 additional South Asian patients, and this will allow study of the association between medical and socio-economic risk factors and acute myocardial infarction at both the individual patient and the site level. These data may also help participating sites evaluate and improve the quality of care that they deliver to future patients. Investigators conducting randomized controlled trials in South Asia should be encouraged to develop opportunistic registries using already established clinical trial networks to generate additional high-quality data at little additional cost.

(ii) More randomized controlled trials with substantial enrollment in South Asian countries are needed to test lifestyle or pharmacologic interventions on patients with (or who are at high risk for) CVD. An important but as yet unanswered research question is the effectiveness of using a polypill (a single pill consisting of a combination of two or more pharmacologic agents proven to reduce CVD risk, including an antiplatelet agent, low doses of a beta-blocker, an angiotensin converting enzyme (ACE)-inhibitor, and a diuretic; as well as a lipid-lowering agent) versus usual care to reduce CHD

events in patients at moderate- to high-risk for CHD. Another question of great interest is whether homocysteine-lowering therapy is effective in reducing CHD events among South Asian individuals with already existing vascular disease. Even though recent trials have demonstrated no overall benefit for homocysteine-lowering therapy in Western populations^{31,32}, questions have been raised regarding the applicability of these results to South Asians living in the Indian subcontinent where fortification of foods with folate is uncommon and population levels of serum homocysteine are on average considerably higher than in the West³³.

(iii) Studies are needed to characterize childhood risk factors in South Asian countries. Obesity among children and adolescents are of particular concern; estimates from the World Health Organization indicate that the prevalence of childhood obesity in some developing countries has increased by 28 per cent in only two years³⁴. Childhood risk factor data specific to the Indian subcontinent are essential if the projected rise in CVD rates among future generations is to be successfully curbed. Most intriguing is the simultaneous presence of children who are obese in families where others are undernourished.

(iv) More research on the prevalence of and risk factors for stroke in South Asian countries must be conducted. Cerebrovascular disease is recognized as a major cause of death and disability in South Asian countries; however, very few large studies of stroke (registries or case-control studies) in South Asians have been conducted. This must be rectified in order to accurately determine the burden of stroke on the health and economy of South Asian countries, so that policy changes can be developed to combat this other important form of CVD.

(v) Data on the prevalence of manifestations of non-atherosclerotic cardiovascular disease should continue to be generated. Increasing attention has been paid to the rising burden of CHD in developing countries over the past decade. However, other

conditions including rheumatic heart disease and tuberculous pericardial disease continue to be important problems in the Indian subcontinent and are at risk of being forgotten in the wake of vascular disease. The Indian subcontinent is a unique region in the world in which several stages of the epidemiologic transition can be observed simultaneously (often in the same region), resulting in CVD from both infectious and atherosclerotic aetiologies co-existing in the same population. Thus, programmes that are developed to address atherosclerotic vascular disease in a certain locale should also be equipped to identify and help treat infectious diseases that afflict the same region.

Recommendations to tackle the CVD epidemic in the Indian subcontinent are summarized (Box).

Conclusion

Cardiovascular disease is the prevailing noncommunicable cause of death and disability in the Indian subcontinent, and will become the prevailing overall cause of mortality among the inhabitants of South Asia in the next 20 yr. The current epidemic and imminent growth are due to the huge burden of CVD risk factors, largely driven by urbanization. Newly emerging studies in which CVD risk factors have been carefully and rigorously measured suggest that traditional biologic and environmental CVD risk factors are sufficient to explain the vast majority of the burden of CVD in the Indian subcontinent. Resources should be directed toward applying the existing knowledge base to

Box. Recommendations to address the CVD epidemic in the Indian subcontinent

Suggested policy interventions:

- (i) Establishment of a national regulatory agency to enforce already existing tobacco control legislation (e.g., the Tobacco Control Act and the World Health Organization's Framework Convention on Tobacco Control).
- (ii) Development of programmes to address the high rates of use of smoked beedies and of smokeless tobacco (chewing tobacco and paan).
- (iii) Implementation of programmes to promote healthy dietary patterns and physical activity in schools and workplaces.
- (iv) Identification of cultural norms that might hinder CVD prevention efforts.

Suggested capacity building measures:

- (i) Development of research infrastructure and training of clinical researchers.
- (ii) Establishment of high-quality national surveillance programmes that document causes of death and disability to guide policy and decision makers.
- (iii) Assessment of the knowledge of the CVD burden in the Indian subcontinent among lay people, health care workers, and policy makers.

Suggested research initiatives:

- (i) Generation of reliable statistics on prevalence and incidence of CVD and its risk factors and CVD-related mortality through the initiation of large cohort studies and trial registries.
- (ii) Randomized controlled clinical trials based in South Asian countries to answer research questions of high relevance to the Indian subcontinent (e.g., effectiveness of the polypill in CVD prevention, homocysteine lowering in subjects with vascular disease).
- (iii) Studies documenting childhood risk factors, such as obesity, in both urban and rural settings.
- (iv) Large registries and case-control studies to document the burden of stroke and its determinants in the Indian subcontinent.
- (v) Continuing efforts to address non-atherosclerotic manifestations of CVD, including rheumatic heart disease and tuberculous pericarditis.

tackle the CVD epidemic in policy, capacity building, and research arenas. Control of the CVD epidemic in the Indian subcontinent is tenable in the foreseeable future, provided that policy makers, the lay public, and health professionals in the India subcontinent acknowledge its potential impact and promptly act to address it.

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