

## Hypertension Vaccine may be a boon to millions in developing world

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**H**ypertension affects around 40% adults aged 25 years and more worldwide, and accounts for 7% of total disability-adjusted life-years. A simple algorithmic program is required to manage hypertension consisting of screening, life style measures, treatment and follow-up, a reliable drug supply and distribution system, and a credible health information system. Despite availability of effective antihypertensive drugs, long term treatment is still costly, tedious, and at the population level rather unsuccessful. Hypertension leaves patients and families with an avoidable heavy economic burden due to failure to control blood pressure. Health policy needs to address gross imbalance between prevention and management by increasing contribution to the preventive programs. During 21st century, the risk factors for morbidity and mortality have been changed, and researchers have started to work upon vaccines against lifestyle diseases like hypertension, diabetes etc. Researchers began experimenting with vaccines against the renin-angiotensin system to control hypertension around six decades ago. The vaccine candidates against hypertension namely ATR12181, pHAV-4Ang IIs, CYT006-AngQb, AngI-R, ATRQβ-001 have shown promising results. A candidate vaccine, CYT006-AngQb, has crossed initial phase and moved into phase 2 trials. However, more human studies in subsequent phases of trials are required to establish the safety and efficacy of anti-hypertensive vaccine. If proved safe and cost effective, a vaccine even with 50% efficacy against hypertension may

protect about 90 million people from hypertension and its heavy economic burden. It can be an appropriate solution for low compliance to antihypertensive drug therapy as well as an avalanche to induce efforts on various chronic disease vaccine development programs.

### Hypertension: A Growing Public Health Challenge

Hypertension is a rapidly expanding global epidemic and is associated with increased morbidity, mortality, and socio-economic burden. Overall prevalence of hypertension is around 40% in adults aged 25 y and more which contributes to about one billion cases worldwide.<sup>1</sup> This has been a substantial public health problem in many developing countries experiencing epidemiological transition from communicable to non-communicable chronic diseases (NCDs).<sup>2,3</sup> The main drivers of epidemiological shift of NCDs are globalization, rapid and uneven urbanization, demographic shifts, and inter- and intra-country migrations – these factors result in alterations in dietary practices, decreased physical activity and changes in other behavioral risk factors. According to the Global Burden of Disease Study 2010, hypertension is the leading risk factor for global disease burden accounting for 7% (95% CI: 6.2–7.7%) of total disability-adjusted life-years (DALYs).<sup>2</sup> It jumped to rank 1 in 2010 from rank 4 in 1990.<sup>4</sup> Mortality due to hypertension increased from 7.29(6.70–7.86) million in 1990 to 9.40 (8.58–10.15) million in 2020 worldwide.<sup>2</sup> The WHO Study on global Aging and adult health (SAGE) in 6

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middle-income countries (China, Ghana, India, Mexico, Russia, and South Africa) documented high prevalence of hypertension varying from 23% (India) to 52% (Russia), with between 30% (Russia) and 83% (Ghana) of hypertensives being undiagnosed prior to the survey and between 35% (Russia) and 87% (Ghana) hypertensives currently taking no treatment<sup>5</sup> Across the WHO regions, hypertension prevalence was highest in Africa (46%; both sexes) while lowest prevalence rates is in the Americas (35%; both sexes).<sup>6</sup>

Almost three quarters of hypertensive patients are expected to live in developing countries by 2025.<sup>7</sup> These countries already have very low level of awareness for raised blood pressure and its consequences.<sup>8</sup> Hypertension is present in 35% of the adult population and accounts for 9.4% of total deaths each year in South East Asia.<sup>9</sup> A recent systematic review (2013) from India reports the prevalence of hypertension among urban and rural population ranged from 13.9 to 46.3% and 4.5 to 58.8%, respectively.<sup>10</sup> According to a recent estimate by Anand et al. the age standardized prevalence (25 y and more) of hypertension in Indian males is 36% (29.7–41.8), females 34.2% (28.6–39.9), and both 35.2% (30.9–35.2).<sup>9</sup> The number of people with hypertension in India is expected to increase from 118.2 million in 2000 to 213.5 million in 2025, with nearly equal numbers of men and women.<sup>11</sup> Taking into account the huge burden of hypertension worldwide, WHO adopted “High Blood Pressure” as theme for World Health Day, 2013.<sup>12</sup>

Considering the increasing burden of hypertension in populations in the developing countries, along with conventional methods of prevention, innovative approaches need to be explored. Vaccines have been one of the major breakthroughs in the history of public health. Indeed, vaccines against viral and bacterial pathogens have substantial contribution in achieving steady increase in life expectancy during last century.<sup>13</sup> During 21st century risk factors for morbidity and mortality have been changed, and researchers have started to work upon vaccines against lifestyle diseases like hypertension, diabetes, cancer.<sup>2</sup> Vaccine against hypertension may be a novel approach to tackle this gigantic

public health problem. In this review, need, basis, available evidences, and scope of hypertension vaccine are discussed.

### **Economic Burden of Hypertension**

Hypertension is the most significant contributor to morbidity and mortality caused by NCDs. In the year 2001, healthcare expenditure due to hypertension accounted for approximately US \$372 billion globally, which represented nearly 10% of overall healthcare expenditures.<sup>14</sup> In the World Bank regions Eastern Europe, Central Asia, South Asia, and Middle East, high blood pressure accounted for 23, 23, 16.2, and 12.3% of the total health expenditures respectively. Considering the prevalent blood pressure levels, the direct costs of raised blood pressure were expected over US\$908 billion globally in the current decade.<sup>14</sup> Low compliance to treatment remains a major public health problem in developing countries which again increases the cost of management of hypertension and related consequences.<sup>15</sup> Moreover, indirect costs of high blood pressure can rise to US \$3600 billion annually which is not less than total gross domestic product (GDP) of Germany (5th largest economy of world).<sup>14</sup>

In 2004, the cardiovascular diseases and hypertension contributed to more than one-third of all income losses (US \$22 billion) by NCDs in India. All caregivers and sick individuals aged 15 y and above productively yielded an annual income loss from hypertension of approximately US\$4.4 billion in the same year. Nearly US \$18 billion were spent as out of pocket (OOP) on health care expenses, amounting to 3.3% of India's GDP for that year. Of the total OOP on health, only hypertension contributed around 5.6% fraction (~US \$1 billion). Most of OOP expenditure spent on hypertension is for therapeutic purposes (64%).<sup>16</sup> The rising disease burden and risk factors will both put strain on services delivery and stress budgets in future. Reorientation of health care services toward efficient NCD prevention and control measures is a possible solution.<sup>17</sup> However, currently available antihypertensive drugs barred the life threatening complications of malignant hypertension; the long-term treatment is

still costly, tiresome, and at the population level rather unsuccessful. Still the disturbing fact is that pharmacologic control of blood pressure in the hypertensive patients falls short of nullifying the cardiovascular risk to the level of normotensive persons. Taking into account these shortcomings, either permanent curative remedy or long-term prevention of the hypertension is desperately awaited.

### **Vaccine May be an Alternative**

Developing countries require a simple algorithmic program to manage hypertension. It consists of screening, treatment and follow-up, a reliable and free or subsidized drug supply and distribution system, and a credible health information system (e.g., mortality surveillance).<sup>18</sup> Simultaneously, lifestyle measures (including body weight reduction, adopt DASH (Dietary Approaches to Stop Hypertension) eating plan, dietary sodium reduction, physical activity, moderation of alcohol consumption) to reduce blood pressure, health education about hypertension and cardiovascular diseases, community programs aiming self-referral for risk assessment, and targets for and monitoring of the effect of intervention programs are necessary chores.<sup>19</sup> However, data indicates that prevention and control of hypertension has not yet received due attention in society. Despite the availability of effective treatment, over half of the hypertensive patients give up treatment entirely within a year of diagnosis. Of those who remain under treatment only about 50% have at least 80% of their prescribed drugs. Consequently, because of poor adherence to antihypertensive treatment, approximately 75% of patients with a diagnosis of hypertension do not achieve optimum blood-pressure control.<sup>20</sup> The failure to control hypertension takes an avoidable heavy economic burden on patients and their families.<sup>15</sup>

In addition, there is an enigma at the core of health policy for hypertension. Health policy needs to redress gross imbalance between inadequate prevention and effective management by increasing contribution to the prevention programs.<sup>21</sup> The current approaches are based around the premise of altering human behaviors and lifestyles. These factors include

behaviors which prevent development of hypertension (diet, physical activity, tobacco, stress). Also these include behaviors for effective management of hypertension (initial treatment seeking, treatment initiation, compliance) since the treatment once initiated is lifelong. Like any other behavior change intervention, the gains of such intervention are slow.

The basic lure of vaccines lies therein since once complete cycle of vaccination yields more benefits than what may be achieved by multiple periods of sustained behavior change communication. Vaccines are being considered as attractive alternative to drug therapies because of undesirable side effects and poor compliance associated with drugs.<sup>22</sup> Research on vaccine development should be given priority because it does have lesser compliance because of only single or few doses. Vaccines under trials are generating hopes to ease the high burden of hypertension and related cardiovascular diseases.

### Molecular Basis for Vaccine

The extensively studied renin-angiotensin-aldosterone system (RAAS) is probably the most important regulator of systemic blood pressure. The renin enzyme is formed and released by granular cells in renal afferent arterioles. Renin has a function of cleaving angiotensin I (AngI) from angiotensinogen; AngI is then converted by Angiotensin Converting Enzyme (ACE) to the biologically active angiotensin II (AngII). AngII increases blood pressure levels via a vasoconstriction effect and also by direct (enhancing sodium reabsorption in the proximal tubule) and indirect (stimulating aldosterone production) effects that promote salt retention.<sup>23</sup> Ang II plays an important role in this system; it causes strong vasoconstriction and increases blood pressure by binding with the Ang II type I receptor (AT<sub>1a</sub> Receptor) on the cell surface. Ang II is composed of 8 amino acid residues that the host cannot recognize and induce an immune response for this weak immunogenicity.<sup>24</sup>

### Historical Vignette

Researchers began experimentation with vaccines against the renin-angiotensin

system around 60 y ago. Work on anti-hypertensive vaccines was started in 1951, when Gold blatter al.conducted the first human study on renin vaccine by injecting hog renin into human subjects. Patients with primary hypertension developed antibodies against renin, but failed to achieve reduced blood pressure.<sup>25</sup> After this failure, many vaccine trials were undertaken in animal models using renin from different species, which cause a significant reduction in blood pressure; but these vaccine were unable to reduce blood pressure in humans.<sup>26-29</sup> (Also see Table 1)

However along with some failures, studies have shown hopes for vaccine against hypertension. Angiotensin vaccination strategy is being revisited for managing hypertension in the hope that new conjugates of Ang I and Ang II will produce antibodies of sufficient titer and affinity to control blood pressure in hypertensive patients.

### Vaccines Under Development

In this section, the vaccines candidates those are providing favorable results are discussed. The vaccine candidates viz. ATR12181, pHAV-4Ang IIs, CYT006-AngQb, AngI-R, ATRQB-001 have been given promising results.

The ATR12181 vaccine was formulated in 2006 by peptide from rat AT<sub>1a</sub> receptor in combination with Freund's adjuvant in China. The vaccine was given repeatedly at 0, 4, 8, 12, 16, 24, 32, 40, and 52 wk to spontaneous hypertensive rats (SHRs). This vaccine caused reduction of systolic blood pressure (17 mmHg) in SHRs at 64 wk; however diastolic blood pressure did not achieve target level. It significantly reduced left ventricular (LV) hypertrophy and LV fibrosis in the SHRs before sacrifice. ATR12181 vaccine was found safe in preclinical studies as it caused attenuation of kidney injuries. Morphological examinations of main vital organs such as heart, kidneys, lungs, brain, and liver did not find any signs of autoimmune injuries (Table 1).<sup>38,39</sup>

Xia Ou et al. tested a novel anti-hypertension vaccine in 20 SHRs in China. This vaccine was invented by integrating the expression of Ang II and hepatitis A virus-like particle (HAVLP); and

named it, pHAV-4Ang IIs. This vaccine caused reduction in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) by approximately 23 mmHg and 12 mmHg respectively at 8th week. It induced high titer of Ang II-specific IgG antibody for almost 10 wk. The titer started to reduce at 10th week, then SHRs in the study were sacrificed at 12th week (Table 1).<sup>40</sup>

Cytos Biotechnology developed an AngII specific vaccine (CYT006-AngQb) which is the most promising vaccine candidate currently. It is composed of an AngII peptide with an N-terminal Cys-Gly-Gly extension that is covalently coupled to virus-like particles (VLP). VLP is derived from the coat protein of the bacteriophage Qb. This vaccine reduced SBP in SHRs and was safe in phase 1 clinical trial.<sup>41</sup> A multicenter, double-blind, randomized, placebo-controlled phase IIa trial of this vaccine candidate was conducted in Switzerland on 72 patients with mild-to-moderate hypertension during the year 2008. The vaccine was given at 0, 4, and 12 wk. At a dose of 300 µg, this vaccine decreased mean ambulatory daytime blood pressure at week 14 by -9.0/-4.0 mmHg. This also significantly reduced the early morning blood-pressure rise compared with placebo. The early morning blood pressure surge that occurs during 5-8 AM (the period when the majority of cardiovascular events occur), the 300 µg group experienced a reduction in blood pressure of 25 mmHg for systolic and 13 mmHg for diastolic blood pressure relative to placebo. Vaccination with CYT006-AngQb was associated with no serious adverse events. The vaccine induced a strong angiotensin II specific IgG response in humans and remains the only anti-hypertension vaccine so far that has demonstrated clinical efficacy. Antibody titer peaked after the second dose and again 2 wk after the third dose, but did not exceed the levels attained after the second dose. The average half-life after the third injection was 17 wk (Table 1).<sup>42</sup> Further two phase II, double-blind, placebo-controlled clinical trials were ongoing at time of this publication. Sixty patients with mild-to-moderate hypertension were to receive five injections of CYT-006-AngQb (300 µg subcutaneous)

**Table 1.** Summary of important preclinical and clinical trials of vaccines against hypertension

Author (Year)	Type of vaccine	Phase of trial	Sample size	Location	Outcome
Graham et al. (1970) <sup>30</sup>	Ang II with Bovine serum albumin/ Freund's adjuvant	Preclinical	12 rabbits	United Kingdom	No decrease in blood pressure resulted in termination of trial.
Michel JB et al. (1987, 1990) <sup>31,32</sup>	Pure human renin with Freund's adjuvant	Preclinical	10 SHRs, 10 normotensive rats, and 8 male marmosets	France	High titer of renin antibodies and significant decrease in systolic blood pressure but development of an autoimmune disease localized in the kidney caused termination of the trial.
Reade R et al. (1989) <sup>33</sup>	Ang1 vaccine coupled with Limulus polyphemus hemocyanin	Preclinical	50 SHRs	France	Raised antibody titer, but did not reduce blood pressure.
Gardiner SM et al. (2000) <sup>34</sup>	AngI analog conjugated with a tetanus toxoid carrier protein and adjuvanted with aluminum hydroxide (PMD-2850)	Preclinical	82 male, Sprague-Dawley rats	England	Pressor responses to AngI were significantly inhibited but responses to AngII were unaffected.
Downham MR et al. (2003) <sup>35</sup>	AngI analog vaccine conjugated with keyhole limpet hemocyanin (PMD3117) and PMD-2850 vaccine	Phase 1 clinical trial	12 male, Sprague-Dawley rats and 50 healthy, male, human volunteers	United Kingdom	Both showed anti-AngI responses but did not cause reduction in blood pressure.
Brown M et al. (2004) <sup>36</sup>	PMD3117 vaccine	Phase 2 clinical trial Randomized double-blind placebo-controlled	27 patients with essential hypertension	United Kingdom	Only PMD3117 vaccine evidenced blockade of the renin system and rise in antibody titer but not influenced blood pressure
Zhu et al. (2006) <sup>39</sup>	AngII-type 1A receptor (ATR12181) with TT/ Freund's adjuvant	Preclinical	12 SHRs	China	Repeated immunization lowers blood pressure, decreases cardiac hypertrophy. No auto-immune disease detected
Tissot et al. (2008) <sup>42</sup>	AngII (AngQb) with VLP/ ALOH	Phase 2 clinical trial	72 patients with mild to moderate hypertension	Switzerland	Significant blood pressure decrease in mean blood pressure. Safe, tolerable, and long half-life (4 mo).
Turkie WH et al. (2010) <sup>37</sup>	Angiotensin therapeutic vaccine (ATV) by using novel adjuvant, CoVaccine HT™	Phase 2b clinical trial Randomized, double blind, placebo controlled	124 patients with mild to moderate hypertension	United Kingdom	Terminated due to dose limiting adverse effects.
Hong F et al. (2011) <sup>43</sup>	Antiangiotensin peptide AngI-R	Preclinical	27 SHRs	China	Decrease the blood pressure of SHRs, increase in anti-AngI/II antibody titer.
Chen et al. (2013) <sup>44</sup>	Human angiotensin II (Ang II) receptor type 1 conjugated with Qβ bacteriophage virus-like particles	Preclinical	40 mice, 36 SHRs	China	Decreased the blood pressure of Ang II-induced hypertensive mice and spontaneously hypertensive rats effectively.
Ou X et al. (2013) <sup>40</sup>	chimeric protein named pHAV-4Ang IIs	Preclinical	20 SHRs	China	Decrease blood pressure in SHRs

\*SHRs, spontaneous hypertensive rats; VLP, virus like particle; ALOH, aluminum hydroxide; pHAV, protein hepatitis A virus.

or placebo (no treatment period specified). The primary outcome measures for this trial are adverse events, and secondary outcome measures are changes in

daytime, night-time, and 24 h ambulatory blood pressure; titer of IgG specific for AngII; and concentrations of plasma renin, AngII and aldosterone over 24 h.

In the second trial, 80 patients with mild-to-moderate hypertension were to receive injections of CYT-006-AngQb (subcutaneous, no dose specified) or placebo (no

treatment period specified). The primary and secondary endpoints are the same as those for the previous trial.<sup>23</sup> Results of the both trials are awaited.

A new vaccine was devised in China by modifying endogenous peptide AngI, called “AngI-R” and covalently conjugating to bovine serum albumin. Aluminum hydroxide was used as an adjuvant to vaccine. Only single dose of this vaccine caused significant decrease in the systolic blood pressure (-15 mmHg) of 27 SHR at 16 wk in a trial conducted in 2011. The anti-hypertensive effect lasted for over one month and caused substantial rise in both anti-AngI/II antibody titer. The antibody response to the vaccine was reversible with a half-life of over 4 wk. This vaccine candidate was found safe, as it did not cause any adverse effect to SHRs (Table 1).<sup>43</sup>

Recently another vaccine ATRQβ-001 was used in animal models (Ang II-induced hypertensive Balb/c mice and SHRs) in China. This vaccine was developed from a peptide (ATR-001) derived from human Ang II receptor type 1 conjugated with Qβ bacteriophage VLPs. ATRQβ-001 vaccine significantly decreased the blood pressure of Ang II-induced hypertensive mice up to 35 mmHg and that of SHRs up to 19 mmHg. The half-life of the anti-ATR-001 antibody was 14.4 d, more than any available antihypertensive drug and peak of antibody titer was at 42 d. This vaccine prevented remodeling of vulnerable hypertensive target organs. No significant immunological damage was detected in experimental animals (Table 1).<sup>44</sup>

Fortunately new conjugates of Ang 1 and Ang 2 did not show immune mediated reactions. These candidate vaccines have shown variable reduction in blood pressure.

### Future Prospects

A candidate vaccine against hypertension, CYT006-AngQb, has crossed initial phase and moved into phase 2 trials.<sup>42</sup> In this stage, more trials involving human subjects are needed to establish the safety and efficacy of anti-hypertensive vaccine, under development.<sup>38,40,43,44</sup> The vaccines prove to be safe and cost-effective in the long run; would step-up the control of

hypertension. If we are able to achieve the control of hypertension worldwide, it could save nearly \$100 billion in health-care expenditures over a 10-y period.<sup>13</sup> In India alone, an effective vaccine even with 50% efficacy against hypertension may protect about 90 million people from hypertension and its consequences, and heavy economic burden.

Vaccines have been one of the most effective and efficient public health tools to reduce morbidity and mortality due to infectious diseases since decades.<sup>45</sup> However, introduction of the vaccine against hypertension in immunization programs will depend not only on the development of an efficacious vaccine but also on many other factors such as cost-effectiveness, efficacy when co-administered with routinely provided vaccines, scope of integration with ongoing vaccination programs and acceptability in community.<sup>46</sup> There is a need for individual and population level safety studies so as not to repeat situations like human papilloma virus vaccines, which had serious ethical irregularities.<sup>47</sup> Financial obstacle will be similar to the HPV vaccines launching in a developing country like India.<sup>48</sup> After crossing all these hurdles, it may prove a miracle therapy in developing countries that would protect populations from their incapability to bear heavy cost of long-term treatments and debilitating complications. It could be a ripe solution for low compliance to antihypertensive drug therapy. Also a successful anti-hypertension vaccine can encourage efforts on various chronic disease vaccine development programs. Hence, an efficient and safe vaccine for hypertension would represent a great public health advance.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### References

1. World Health Organization. Global status report on noncommunicablediseases 2010. Geneva: WHO; 2011.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380:2224-60; PMID:23245609; [http://dx.doi.org/10.1016/S0140-6736\(12\)61766-8](http://dx.doi.org/10.1016/S0140-6736(12)61766-8)

3. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998; 97:596-601; PMID:9494031; <http://dx.doi.org/10.1161/01.CIR.97.6.596>
4. Institute of Health Metrics & Evaluation. GBD 2010 change in leading causes and risks between 1990 and 2010. (Accessed on July 21, 2013) Available from: <http://www.healthmetricsandevaluation.org/gbd/visualizations/gbd-2010-change-leading-causes-and-risks-between-1990-and-2010?metric=DALY>
5. Basu S, Millett C. Social epidemiology of hypertension in middle-income countries: determinants of prevalence, diagnosis, treatment, and control in the WHO SAGE study. *Hypertension* 2013; 62:18-26; PMID:23670299; <http://dx.doi.org/10.1161/HYPERTENSIONAHA.113.01374>
6. World Health Organization. Global Health Observatory (GHO): Raised blood pressure situation and trends. Geneva: WHO; 2013. (Accessed April 24, 2013). Available from: [http://www.who.int/gho/ncd/risk\\_factors/blood\\_pressure\\_prevalence\\_text/en/](http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/)
7. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365:217-23; PMID:15652604
8. Ogah OS, Okpechi I, Chukwuonye II, Akinyemi JO, Onwubere BJC, Falase AO, et al. Blood pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review. *World J Cardiol* 2012;4:327-40. (Accessed on August 28, 2013) Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3530788/>
9. Krishnan A, Garg A, Kahandaliyanage A. Hypertension in the South East Asia Region: an overview. *Regional Health Forum* 2013;17:7-14.
10. Devi P, Rao M, Sigamani A, Faruqui A, Jose M, Gupta R, Kerkar P, Jain RK, Joshi R, Chidambaram N, et al. Prevalence, risk factors and awareness of hypertension in India: a systematic review. *J Hum Hypertens* 2013; 27:281-7; PMID:22971751; <http://dx.doi.org/10.1038/jhh.2012.33>
11. Reddy KS. Regional case studies-India. Nestle Nutr Workshop Ser Pediatr Program. 2009;63:15-24; discussion 41-6, 259-68.
12. World Health Organization. World Health Day - 7 April 2013. Geneva: WHO; 2013.
13. Rappuoli R, Mandl CW, Black S, De Gregorio E. Vaccines for the twenty-first century society. *Nat Rev Immunol* 2011; 11:865-72; PMID:22051890
14. Gaziano TA, Bitton A, Anand S, Weinstein MC; International Society of Hypertension. The global cost of nonoptimal blood pressure. *J Hypertens* 2009; 27:1472-7; PMID:19474763; <http://dx.doi.org/10.1097/HJH.0b013e328232a9ba3>
15. Osamor PE, Owumi BE. Factors associated with treatment compliance in hypertension in southwest Nigeria. *J Health Popul Nutr* 2011; 29:619-28; PMID:22283036
16. Mahal A, Karan A, Engelgau M. 3. The economic implications of non-communicable disease for India. Health, nutrition and population (HNP) discussion paper. Washington: The World Bank; 2010 (Accessed on May 2013). Available from: <http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1095698140167/EconomicImplicationsofNCDforIndia.pdf>
17. Engelgau MM. Sameh El-Saharty, Kudesia P, Rajan V, Rosenhouse S, Okamoto K. Capitalizing on the demographic transition: tackling noncommunicable diseases in South Asia. Washington DC: World Bank;2011. (Accessed on June 23, 2013). Available from: [http://www-wds.worldbank.org/external/default/WDSContentServer/IW3P/IB/2011/08/17/000333038\\_20110817004056/Rendered/PDF/622600REPLACEMENT00use0same0info.pdf](http://www-wds.worldbank.org/external/default/WDSContentServer/IW3P/IB/2011/08/17/000333038_20110817004056/Rendered/PDF/622600REPLACEMENT00use0same0info.pdf)

18. Perkovic V, Huxley R, Wu Y, Prabhakaran D, MacMahon S. The burden of blood pressure-related disease: a neglected priority for global health. *Hypertension* 2007; 50:991-7; PMID:17954719; <http://dx.doi.org/10.1161/HYPERTENSIONAHA.107.095497>
19. National Heart, Lung, and Blood Institute, National Institutes of Health, U. S. Department of Health and Human Services. JNC 7 Express. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Bethesda, MD: National Institutes of Health; 2003. NIH Publication No. 03-5233.
20. Sabaté E, ed. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
21. Redwood H. Hypertension, society and public policy. *Eur Heart J Suppl* 2007; 9:B13-8; <http://dx.doi.org/10.1093/eurheartj/sum003>
22. Elliott WJ. The economic impact of hypertension. *J Clin Hypertens (Greenwich)* 2003; 5(Suppl 2):3-13; PMID:12826765; <http://dx.doi.org/10.1111/j.1524-6175.2003.02463.x>
23. Phisitkul S. CYT-006-AngQb, a vaccine against angiotensin II for the potential treatment of hypertension. *Curr Opin Investig Drugs* 2009; 10:269-75; PMID:19333885
24. Ou X, Guo L, Wu J, Mi K, Yin N, Zhang G, Li H, Sun M. Construction, expression and immunogenicity of a novel anti-hypertension angiotensin II vaccine based on hepatitis A virus-like particle. *Hum Vaccin Immunother* 2013; 9:1191-9; PMID:23412424; <http://dx.doi.org/10.4161/hv.23940>
25. Goldblatt H, Haas E, Lamfrom H. Antirenin in man and animals. *Trans Assoc Am Physicians* 1951; 64:122-5; PMID:14884242
26. Slater EE, Corvol P, Menard J, Burton J, Hartley LH. Antisera to human renin normalize renin-dependent hypertension in the monkey: therapeutic implications. *Clin Exp Hypertens A* 1984; 6:923-37; PMID:6203672; <http://dx.doi.org/10.3109/10641968409044047>
27. Wood JM, Heusser C, Gulati N, Forgiarini P, Hofbauer KG. Monoclonal antibodies against human renin. Blood pressure effects in the marmoset. *Hypertension* 1986; 8:600-5; PMID:3013776; <http://dx.doi.org/10.1161/01.HYP.8.7.600>
28. Deodhar SD, Haas E, Goldblatt H. Production of antirenin to homologous renin and its effect of experimental renal hypertension. *J Exp Med* 1964; 119:425-32; PMID:14129713; <http://dx.doi.org/10.1084/jem.119.3.425>
29. Helmer OM. Studies on renin antibodies. *Circulation* 1958; 17:648-52; PMID:13523774; <http://dx.doi.org/10.1161/01.CIR.17.4.648>
30. Macdonald GJ, Louis WJ, Renzini V, Boyd GW, Peart WS. Renal-clip hypertension in rabbits immunized against angiotensin II. *Circ Res* 1970; 27:197-211; PMID:4318416; <http://dx.doi.org/10.1161/01.RES.27.2.197>
31. Michel JB, Guettier C, Philippe M, Galen FX, Corvol P, Ménard J. Active immunization against renin in normotensive marmoset. *Proc Natl Acad Sci U S A* 1987; 84:4346-50; PMID:3108891; <http://dx.doi.org/10.1073/pnas.84.12.4346>
32. Michel JB, Sayah S, Guettier C, Nussberger J, Philippe M, Gonzalez MF, Carelli C, Galen FX, Menard J, Corvol P. Physiological and immunopathological consequences of active immunization of spontaneously hypertensive and normotensive rats against murine renin. *Circulation* 1990; 81:1899-910; PMID:2188756; <http://dx.doi.org/10.1161/01.CIR.81.6.1899>
33. Reade R, Michel JB, Carelli C, Huang H, Baussant T, Corvol P. [Immunisation of spontaneously hypertensive rats against angiotensin II]. *Arch Mal Coeur Vaiss* 1989; 82:1323-8; PMID:2510667
34. Gardiner SM, Auton TR, Downham MR, Sharp HL, Kemp PA, March JE, Martin H, Morgan PJ, Rushton A, Bennett T, et al. Active immunization with angiotensin I peptide analogue vaccines selectively reduces the pressor effects of exogenous angiotensin I in conscious rats. *Br J Pharmacol* 2000; 129:1178-82; PMID:10725266; <http://dx.doi.org/10.1038/sj.bjp.0703178>
35. Downham MR, Auton TR, Rosul A, Sharp HL, Sjöström L, Rushton A, Richards JP, Mant TG, Gardiner SM, Bennett T, et al. Evaluation of two carrier protein-angiotensin I conjugate vaccines to assess their future potential to control high blood pressure (hypertension) in man. *Br J Clin Pharmacol* 2003; 56:505-12; PMID:14651724; <http://dx.doi.org/10.1046/j.1365-2125.2003.01926.x>
36. Brown MJ, Coltart J, Gunewardena K, Ritter JM, Auton TR, Glover JF. Randomized double-blind placebo-controlled study of an angiotensin immunotherapeutic vaccine (PMD3117) in hypertensive subjects. *Clin Sci (Lond)* 2004; 107:167-73; PMID:15040783; <http://dx.doi.org/10.1042/CS20030381>
37. Safety and efficacy study of angiotensin therapeutic vaccine in subjects with mild to moderate hypertension. (Accessed May 4, 2013). Available from: <http://clinicaltrials.gov/show/NCT00702221>
38. Zhu F, Liao YH, Liudong L, Wei YM, Wang M, Chen M, et al. Observation of long-term efficacy and safety of an ATR12181 vaccine against hypertension in SHR. *Circulation*. 2006;114 (18 suppl):II-575. Abstract 2753. (Accessed May 3, 2013). Available from: [http://circ.ahajournals.org/cgi/content/meeting\\_abstract/114/18\\_MeetingAbstracts/II\\_575-c](http://circ.ahajournals.org/cgi/content/meeting_abstract/114/18_MeetingAbstracts/II_575-c)
39. Zhu F, Liao YH, Li LD, Cheng M, Wei F, Wei YM, Wang M. Target organ protection from a novel angiotensin II receptor (AT1) vaccine ATR12181 in spontaneously hypertensive rats. *Cell Mol Immunol* 2006; 3:107-14; PMID:16696897
40. Ou X, Guo L, Wu J, Mi K, Yin N, Zhang G, Li H, Sun M. Construction, expression and immunogenicity of a novel anti-hypertension angiotensin II vaccine based on hepatitis A virus-like particle. *Hum Vaccin Immunother* 2013; 9:1191-9; PMID:23412424; <http://dx.doi.org/10.4161/hv.23940>
41. Ambühl PM, Tissot AC, Fulurija A, Maurer P, Nussberger J, Sabat R, Nief V, Schellekens C, Sladko K, Roubicek K, et al. A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity. *J Hypertens* 2007; 25:63-72; PMID:17143175; <http://dx.doi.org/10.1097/HJH.0b013e32800ff5d6>
42. Tissot AC, Maurer P, Nussberger J, Sabat R, Pfister T, Ignatenko S, Volk HD, Stocker H, Müller P, Jennings GT, et al. Effect of immunisation against angiotensin II with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomised, placebo-controlled phase IIa study. *Lancet* 2008; 371:821-7; PMID:18328929; [http://dx.doi.org/10.1016/S0140-6736\(08\)60381-5](http://dx.doi.org/10.1016/S0140-6736(08)60381-5)
43. Hong F, Quan WY, Pandey R, Yi S, Chi L, Xia LZ, Yuan M, Ming L. A vaccine for hypertension based on peptide AngI-R: a pilot study. *Int J Cardiol* 2011; 148:76-84; PMID:19932924; <http://dx.doi.org/10.1016/j.ijcard.2009.10.027>
44. Chen X, Qiu Z, Yang S, Ding D, Chen F, Zhou Y, Wang M, Lin J, Yu X, Zhou Z, et al. Effectiveness and safety of a therapeutic vaccine against angiotensin II receptor type 1 in hypertensive animals. *Hypertension* 2013; 61:408-16; PMID:23184378; <http://dx.doi.org/10.1161/HYPERTENSIONAHA.112.201020>
45. Bairwa M, Rajput M, Khanna P, Rohilla R, Verma R, Chawla S. Malaria vaccine: a bright prospect for elimination of malaria. *Hum Vaccin Immunother* 2012; 8:819-22; PMID:22739688; <http://dx.doi.org/10.4161/hv.20145>
46. World Health Organization. Introducing a vaccine: policy and programme considerations. (Accessed on September 28, 2013) Available from: [http://www.who.int/nuvi/Vaccine\\_intro\\_resources/en/](http://www.who.int/nuvi/Vaccine_intro_resources/en/)
47. Shetty P. Vaccine trial's ethics criticized. *Nature* 2011; 474:427-8; PMID:21697918; <http://dx.doi.org/10.1038/474427a>
48. Kaarthigeyan K. Cervical cancer in India and HPV vaccination. *Indian J Med Paediatr Oncol* 2012; 33:7-12; PMID:22754202; <http://dx.doi.org/10.4103/0971-5851.96961>