HEART
HEALTH & EDUCATION ADVICE & RESOURCE TEAM

Helpdesk Report: **Affordability of Non-Communicable Disease (NCD) prevention**

Date: 26 September 2014

Query: Produce a report looking at evidence about the affordability of managing NCDs either through primary or secondary prevention in low income countries.

Content

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1. Overview

The WHO (2013) *Global action plan for the prevention and control of non-communicable diseases, 2013-2020* outlines a combination of population-wide and individual interventions for prevention and control of Non-Communicable Diseases (NCDs) deemed to be 'very cost-effective'. They estimate the cost of this, in terms of current health spending, to be 4% in low-income countries, 2% in lower middle-income countries and less than 1% in upper middle-income and high-income countries. Highlighted as affordable are:

- Tobacco: increasing pricing, creating smoke-free laws, health warnings/media campaigns, banning advertising.
- Alcohol: regulating availability, restricting advertising, taxation.
- Health, diet and activity: reducing salt, replacing trans fats with unsaturated fats, public awareness programmes.
- Cardiovascular disease (CVD) and diabetes prevention: Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling for high-risk individuals.
- Cancer prevention: Hepatitis B immunisation, cervical cancer screening.

Some cost estimates for specific interventions are identified in the literature:

- Bovet & Paccaud (2012) refer to estimated yearly costs per head for six different prevention packages for Brazil, China, India, Mexico and South Africa.
- Reduced salt intake intervention and the four WHO tobacco control provisions could be implemented for less than USD $0.40 per person per year in Low and Middle Income Countries (LMICs) (Bovet & Paccaud, 2012).
- Jafar et al. (2011) outline different costs for blood pressure control for hypertensive subjects in Pakistan: combined home health education (HHE) plus trained GP ($3.99); HHE only ($3.34); and trained GP only ($0.65).

- Pascal (2015) reported some costs from a 2013 price guide: Aspirin for CVD prevention (monthly cost $0.084), Simvastatin for stroke prevention (monthly cost $0.705), Atenolol to prevent cardiac complications (monthly cost $0.354).
- Costs identified by Mendis & Chestnov (2013) include: four population-based demand reduction measures for tobacco control, US$ 0.11 per head of population for low- and middle income countries; three interventions for reducing harmful alchohol use in Africa, US$ 0.14 per person; and three interventions for health diet and exercise in Africa, less than US$ 0.10 per person.

Affordability for secondary CVD prevention can be referred to in terms of the number of days wages required for the lowest-paid government worker to buy a one-month supply. Mendis et al. (2007) report a one-month supply of standard generic secondary prevention drugs cost 1.5 days wages of the lowest-level government worker in Sri Lanka; more than 5 days' wages in Brazil, Nepal, and Pakistan; and more than 18 days' wages in Malawi. They suggest prices could be reduced by improving purchasing efficiency, eliminating taxes and regulating mark-ups. Combination drugs such as polypills could improve affordability. Lonn et al (2010) suggest costs of a polypill using generic components (estimated at ≈$1 a day in developed and <20 cents in developing countries) are likely to be much lower than the costs of individual drugs. Sanz & Fuster (2009) recommend a polypill including uncoated aspirin to reduce formulation complexity.

Literature was identified on the use of a vaccine for the human papillomavirus (HPV), the leading cause of cervical cancer. The Gavi Alliance is supporting the introduction of vaccines to make it more affordable, US$ 4.50 per dose.

2. Studies on multiple prevention strategies

Global action plan for the prevention and control of non-communicable diseases, 2013-2020
WHO (2013)
http://apps.who.int/iris/bitstream/10665/94384/1/9789241506236_eng.pdf

For all countries, the cost of inaction far outweighs the cost of taking action on non-communicable diseases (NCDs) as recommended in this action plan. There are interventions for prevention and control of NCDs that are affordable for all countries and give a good return on investment, generating one year of healthy life for a cost that falls below the gross domestic product (GDP) per 1 person and are affordable for all countries. The total cost of implementing a combination of very cost-effective population-wide and individual interventions, in terms of current health spending, amounts to 4% in low-income countries, 2% in lower middle-income countries and less than 1% in upper middle-income and high-income countries.

A selection of initiatives are highlighted to be very cost-effective and affordable for all countries according to WHO estimates. However, they have not been assessed for specific contexts of individual countries.

The highlighted initiatives for tobacco use are:
- Reduce affordability of tobacco products by increasing tobacco excise taxes
- Create by law completely smoke-free environments in all indoor workplaces, public places and public transport
- Warn people of the dangers of tobacco and tobacco smoke through effective health warnings and mass media campaigns
- Ban all forms of tobacco advertising, promotion and sponsorship

Interventions highlighted for prevention of harmful alcohol use:

- Regulating commercial and public availability of alcohol
- Restricting or banning alcohol advertising and promotions
- Using pricing policies such as excise tax increases on alcoholic beverages

To promote healthy diet and activity:
- Reduce salt intake
- Replace trans fats with unsaturated fats
- Implement public awareness programmes on diet and physical activity

There is one policy option highlighted as affordable for the prevention of CVD and diabetes:
- Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals who have had a heart attack or stroke and to persons with high risk (≥ 30%) of a fatal and nonfatal cardiovascular event in the next 10 years.

Cost-effective and affordable policy options for cancer prevention:
- Prevention of liver cancer through hepatitis B immunization
- Prevention of cervical cancer through screening (visual inspection with acetic acid [VIA] (or Pap smear (cervical cytology), if very cost-effective), linked with timely treatment of pre-cancerous lesions

Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings
WHO (2013)
http://apps.who.int/iris/bitstream/10665/133525/1/9789241506557_eng.pdf?ua=1

This document includes description of a new financial planning tool developed by the World Health Organization (WHO) to assist low- and middle income countries in scaling up a core set of interventions to tackle NCDs, such as heart disease and stroke, diabetes, cancer and chronic lung disease.

It is a tool for financial planning (over the period 2011-2025) that can be used to forecast resource needs at national and sub-national levels. The tool can enhance traditional budgeting mechanisms in countries and provide new information to development agencies about the resources needed to tackle the growing burden of NCDs.

The tool has been used to produce a 'price tag' for a combined set of population-based and individual-level 'best buy' NCD interventions that have been identified as priority actions by WHO. The average yearly cost for all low- and middle-income countries is estimated to be US$ 11.4 billion (an overall cost of US$ 170 billion over the period 2011-2025).

The cost per head of population is low. It represents an annual investment of under US$ 1 in low-income countries, US$ 1.50 in lower middle-income countries; and US$ 3 in upper middle-income countries. Expressed as a proportion of current health spending, the cost of implementing such a package amounts to 4% in low-income countries, 2% in lower middle-income countries and less than 1% in upper middle-income countries.

Population-based best buy interventions address tobacco and harmful alcohol use, as well as unhealthy diet and physical inactivity in low- and middle-income countries. The cost for these approaches US$ 2 billion yearly. In low-income and lower middle-income countries, the median cost per head of population amounts to less than US$ 0.20 per year, while for upper-middle income countries the median value is close to US$ 0.50. These amounts represent less than 1% of total per capita spending on health.

Individual-based best buy interventions are delivered in primary health care settings and include, for example, counselling and drug therapy for persons with or at high risk of cardiovascular disease, plus measures to prevent cervical cancer. For these interventions the cost averages more than US$ 10 billion yearly. Over the scale-up period 2011-2025, the annual cost per head of population falls below US$ 1 in low-income countries, less than US$ 1.50 in lower-middle income countries and averages US$ 2.50 in upper-middle income countries.

Cardiovascular Disease and the Changing Face of Global Public Health: A Focus on Low and Middle Income Countries
Bovet P & Paccaud F. (2012). Public Health Rev, 33(2), 397-415.
http://www.publichealthreviews.eu/upload/pdf_files/10/00_Bovet.pdf

There are two main strategies for the prevention of NCDs: population wide interventions and individual based interventions. Among interventions targeting the entire population, structural measures aimed at making the healthy choice the easy choice for individuals are particularly attractive. Importantly, structural interventions may not need explicit cooperation of individuals in order to produce the expected lifestyles changes (e.g. improved diet through reformulation of manufactured foods to reduce trans fats or salt). Another advantage of population-wide interventions is that they can be implemented at low cost and some of them can even generate revenue (e.g. taxes on tobacco and on alcohol). On the other hand, individual-level strategies often incur very high costs (e.g. lifelong treatment of hypertension or diabetes), which emphasizes the need to carefully select interventions (e.g. screening strategies, medications, etc.) that are both affordable and highly cost-effective. Selecting interventions based on cost-effectiveness criteria is also important to ensure that the provision of services is not left at the mercy of local and global commercial interests.

Estimated annual cost per head (in US$) of a package for prevention of CVD and other main chronic diseases

	Brazil	China	India	Mexico	South Africa
Tobacco use-excise tax increase, information and labelling, smoking restrictions and advertising bans	0.25	0.14	0.16	0.54	0.6
Harmful alcohol use-excise tax increase, advertising bans, restricted access	0.15	0.07	0.05	0.24	0.29
Unhealthy diet and physical activity: mass media campaigns, food taxes and subsidies, nutritional information/ labelling, and marketing restrictions	0.48	0.43	0.35	0.79	0.99
Reduced dietary salt (mass media campaigns, regulation of the food industry)	0.12	0.05	0.06	0.22	0.15
Combination drug therapy for high-risk individuals	1.89	1.02	0.90	2.74	1.85
Total cost per head of intervention set (excluding cost synergies or future treatment cost savings)	2.89	1.72	1.52	4.53	3.88

(Source: Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo-Barron V, Chisholm D. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. *Lancet*. 2010; 376: 1775-84)

Affordability is essential. In LMICs, it has been estimated that two population-wide interventions (a 15% reduction of salt intake and the implementation of the four key provisions of the Framework Convention on Tobacco Control) could prevent 14 million premature deaths over ten years. These interventions could be implemented for less than USD $0.40 per person per year in LMICs.

Cost-Effectiveness of Community-Based Strategies for Blood Pressure Control in a Low-Income Developing Country, Findings From a Cluster-Randomized, Factorial-Controlled Trial
Jafar TH, Islam M, Bux R, Poulter N, Hatcher J, Chaturvedi N, ... & Cosgrove P. (2011). *Circulation*, 124(15), 1615-1625.
http://circ.ahajournals.org/content/124/15/1615.full

Evidence on economically efficient strategies to lower blood pressure (BP) from LMICs remains scarce. This study examines the cost-effectiveness of different community-based strategies for blood pressure control in Karachi, Pakistan. The Control of Blood Pressure and Risk Attenuation (COBRA) trial randomized 1341 hypertensive subjects in 12 randomly selected communities to 3 intervention programs: (1) combined home health education (HHE) plus trained general practitioner (GP); (2) HHE only; and (3) trained GP only. The comparator was no intervention (or usual care). The reduction in BP was most pronounced in the combined group.

Total costs were assessed at baseline and 2 years to estimate incremental cost-effectiveness ratios based on: (1) intervention cost; (2) cost of physician consultation, medications, diagnostics, changes in lifestyle, and productivity loss; and (3) change in systolic BP. Precision of the incremental cost-effectiveness ratio estimates was assessed by 1000 bootstrapping replications. Bayesian probabilistic sensitivity analysis was also performed. The annual costs per participant associated with the combined HHE plus trained GP, HHE alone, and trained GP alone were $3.99, $3.34, and $0.65, respectively. HHE plus trained GP was the most cost-effective intervention, with an incremental cost-effectiveness ratio of $23 (95 confidence interval, 6–99) per mm Hg reduction in systolic BP compared with usual care, and remained so in 97.7 of 1000 bootstrapped replications.

The combined intervention of HHE plus trained GP is potentially affordable and more cost-effective for BP control than usual care or either strategy alone in some communities in Pakistan, and possibly other countries in Indochina with similar healthcare infrastructure.

Costs, Benefits, and Effectiveness of Interventions for the Prevention, Treatment, and Control of Cardiovascular Diseases and Diabetes in Africa
Mendis S, & Chestnov O. (2013). *Progress in cardiovascular diseases*, 56(3), 314-321.
http://www.sciencedirect.com/science/article/pii/S0033062013001540

The cost of implementing four population-based demand reduction measures for tobacco control (smoke-free policies, raising tobacco taxes, package warnings, advertising bans) is low. Total financial resources required to implement them in all LMICs is projected to be US$ 0.6 billion per year or US$ 0.11 per head of population. Costs include media campaigns and overall program management. Implementation costs vary by income level of countries; the median cost per capita ranges from as little as US$ 0.05 in low-income countries to US$ 0.15 in upper-middle income countries.

The three very cost effective interventions for reducing harmful use of alcohol are restriction of access to retailed alcohol, enforcement of bans on alcohol advertising and raising taxes on alcohol. The cost of implementing them in Africa is US$ 0.14 per person. Core drivers of these costs are media related expenses and human resource costs involved in program management and enforcement of alcohol-related laws and policies.

Three interventions for promoting healthy diet and physical activity that can be categorized as very cost effective include: promoting public awareness about diet and physical activity, reducing salt intake, and replacing trans-fat with polyunsaturated fat. The costs of implementing them are low (less than US$ 0.10 per person in Africa). The largest public

health expenditure involved in implementing these interventions is in relation to health promotion and awareness campaigns using mass media.

Individual interventions for CVD and diabetes treatment and prevention classified as 'quite low cost', less than US$1 per capita are:

- Drug therapy (including glycemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals (≥30 years), who have had a heart attack or stroke and to persons with high risk (≥ 30%) of a fatal and nonfatal cardiovascular event in the next 10 year.
- Aspirin therapy for acute myocardial infarction

Cost effective interventions for the prevention of cardiovascular disease in low and middle income countries: a systematic review
Shroufi A, Chowdhury R, Anchala R, Stevens S, Blanco P, Han T, Niessen L & Franco O H (2013). *BMC public health*, 13(1), 285.
http://www.biomedcentral.com/1471-2458/13/285

This study systematically assesses the evidence on cost-effectiveness for preventive cardiovascular interventions in low and middle-income settings by conducting a systematic review of economic evaluations on interventions for prevention of cardiovascular disease.

Tobacco control
Six studies that evaluated tobacco control interventions in one or more LMICs were identified and reviewed. Although personal interventions such as nicotine replacement therapy (NRT) were generally found to be cost effective across the six studies, population-based interventions were much more cost effective (by an order of 10-100 fold).

Pharmacological primary prevention using an absolute risk based approach
Pharmacological primary prevention involves providing preventive medication to individuals on the basis of absolute risk of developing a disease. Five of seven studies evaluated found this approach to be "very cost" effective or "cost effective". Less favourably, studies in Tanzania and Kyrgyzstan reported borderline and negative results respectively for the cost effectiveness of an absolute risk based approach.

Individual risk factor reduction approach
This approach involves reducing a characteristic or behaviour that increases the probability that a disease will occur. Five studies found the use of drugs to lower "high" blood pressure were found to be in the "very cost effective" or "cost effective" range. In the case of statins, three studies reported them to be cost effective while two studies found them to be not cost effective.

Pharmacological secondary prevention
Pharmacological secondary prevention involves providing medication to reduce the impact of a disease that has already occurred to halt or slow its progress. All three studies found pharmacological secondary prevention of CVD to be in the "cost effective" or "very cost effective" range.

Use of mass media
Five studies evaluated the use of mass media to reduce salt consumption, to stop smoking, to improve dietary characteristics, as well as joint campaigns. The use of mass media was generally found to be "very cost effective".

Other legislative interventions
Four of the studies included reported evaluations of legislative interventions such as the compulsory reduction of salt in food. Interventions of this type were generally found to be

"very cost effective", or "extremely cost effective", with the exception of salt lowering legislation in Sub-Saharan Africa, which was found not to be cost effective.

Comment on data sources
Virtually none of the evaluations are fully based on data derived from LMICs. There was a consistent difference between the sources of the effect estimates for population-based interventions compared to personal interventions, with the latter generally based upon studies lower in the hierarchy of evidence. The effectiveness estimates on personal, pharmacologic interventions for the most part are based on studies with reliable effect sizes in high income countries, supplemented with LMIC cost estimates. The evaluations of population-based interventions lack any RCT level of evidence which leads to greater uncertainties. Whereas individual interventions may be attractive, although based on HIC evidence, this is not the case in the area of tobacco control. Personal interventions such as Nicotine Replacement Therapy (NRT) appear to be far less cost effective than population-based interventions in low-resource settings. There are few trials of population-based interventions in low and middle income countries, leading to a lack of effectiveness information.

3. CVD prevention drugs

Strengthening health systems for the prevention and control of NCDs: some issues for implementation
Bovet P. (2015) PowerPoint presentation. Not available online.

In this presentation some drugs costs MSH International Drug Price Indicator Guide 2013 which are of note:

- Aspirin (ASA) 100mg tab (CVD prevention), monthly cost $0.084
- Simvastatin 20mg tab (Stroke prevention), monthly cost $0.705
- Atenolol 50mg tab (Prevention of cardiac complications), monthly cost $0.354

Fixed-dose combination therapy and secondary cardiovascular prevention: rationale, selection of drugs and target population
Sanz, G., & Fuster, V. (2009). *Nature Clinical Practice Cardiovascular Medicine*, 6(2), 101-110.
http://www.nature.com/nrcardio/journal/v6/n2/full/ncpcardio1419.html#B30

The WHO considers interventions to be cost-effective if the incremental cost ratio is less than three times the gross national income per head. In this study, the authors conclude that a regimen containing aspirin, two antihypertensive drugs and one statin would be considered cost-effective in Asia, Latin America and Africa according to the WHO guidelines.

The fact that secondary prevention medication is cost-effective does not, however, ensure affordability in middle-income and low-income countries. Affordability, defined as the number of days' wages required for the lowest-paid government worker to purchase a 1-month supply of a generic, four-drug, secondary prevention regimen varied among low-income and middle-income countries, and reached 18 days in some. In addition, out-of-pocket expenditure on health is much higher in less developed countries than in developed nations.

The authors believe that a polypill (such as the one they are currently developing), delivered at a low price could improve adherence to treatment, reduce the cost and make treatment affordable in low-income countries. The polypill being developed includes uncoated aspirin to reduce formulation complexity.

The Polypill in the Prevention of Cardiovascular Diseases. Key Concepts, Current Status, Challenges, and Future Directions
Lonn E, Bosch J, Teo KK, Pais P, Xavier D, & Yusuf S. (2010). *Circulation*, *122*(20),2078-2088.
http://circ.ahajournals.org/content/122/20/2078.full (A sponsored study)

Cardiovascular disease (CVD) is the major cause of death and disability globally. The CVD burden has decreased in developed countries as effective prevention and treatment strategies have been implemented. However, CVD has increased in developing countries, and by the year 2020, 80% of the global CVD mortality is predicted to occur in LMICs. Cost and affordability are major barriers in LMICs. Although drugs used in secondary prevention are cost-effective, these drugs are still not affordable to the majority of individuals in middle- and low-income countries, where the cost of a 1-month supply of standard generic secondary prevention drugs ranges from 1.5 to 18.4 days' wages of government workers.

Fixed-dose combination drugs [ie, polypill(s)], especially those based largely on generic preparations, could overcome some, but not all, of these barriers. Furthermore, when combined with new models of healthcare delivery (eg, by nonphysician healthcare workers and with little or no monitoring), the use of the polypill may lead to more widespread and cost-effective secondary prevention.

Costs of a polypill using generic components (estimated at ≈$1 a day in developed and <20 cents in developing countries) are likely to be much lower than the costs of individual drugs. Savings may be realized from reduced packaging, distribution, and marketing costs and fewer physician visits and laboratory tests. An example of potential cost savings is provided by the pricing of the Polycap used in The Indian Polycap Study (TIPS) trial in India, where it is currently approved for use and marketed at a substantially lower cost than its component drugs.

Scaling Up Chronic Disease Prevention Interventions in Lower- and Middle-Income Countries
Gaziano TA, & Pagidipati N. (2013). *Annual review of public health*, 34, 317.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3686269/

Aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), or lipid-lowering drugs can each independently lower the risk of future vascular events in patients with a history of ischemic heart disease by about one-quarter; when they are taken in combination, a reduction in vascular events by two-thirds to three-quarters can be expected. Multidrug regimens for secondary prevention in LMICs have been cost-effective ($350 per Quality-Adjusted Life Year – QALY gained) according to WHO standards, meaning that the intervention would cost less than three times the GNI of these countries.

Given the limited resources, finding low-cost prevention strategies is a top priority. Using prediction rules or risk scores to identify those at higher risk in order to target specific behavioural or drug interventions is a well-established primary prevention strategy and has proven to be cost-effective in developing countries. Most have included age, sex, hypertension, smoking status, diabetes mellitus, and lipid values, whereas others have also included family history.

The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries
Mendis S, Fukino K, Cameron A, Laing R, Filipe Jr, A, Khatib O, Leowski J & Ewen, M. (2007). *Bulletin of the World Health Organization*, 85(4), 279-288.

One month of combination therapy with the lowest-priced generic version of aspirin, a statin, a beta-blocker, and an angiotensin-converting-enzyme inhibitor (ACEI) cost 1.5 days' wages of the lowest-level government worker in Sri Lanka; more than 5 days' wages in Brazil, Nepal, and Pakistan; and more than 18 days' wages in Malawi.

Context-specific policies are required to improve access to essential medicines. Generic products should be promoted by educating professionals and consumers, by implementing appropriate policies and incentives, and by introducing market competition and/or price regulation. Improving governance and management efficiency, and assessing local supply options, may improve availability. Prices could be reduced by improving purchasing efficiency, eliminating taxes and regulating mark-ups.

Prevalence, Awareness, Treatment, and Control of Hypertension in Rural and Urban Communities in High-, Middle-, and Low-Income Countries
Chow CK, et al. (2013) *Jama* 310.9: 959-968.
http://jama.jamanetwork.com/article.aspx?articleid=1734702&resultclick=3

Although low-cost generic blood pressure–lowering medications are available in LICs, possible barriers to use of medications are still affordability (as a proportion of local income), lack of drug inventory, distance to clinics, and the costs to see physicians. Hence, models of care that shift the detection and initial treatment of hypertension to nonphysician health workers should be considered. Effectiveness of these models of care have been demonstrated in management of other conditions such as HIV in developing countries. However, even among individuals who have received treatment, there is poor blood pressure control. This suggests ineffectiveness in current treatment approach, which is largely based on the use of single drugs. Instead, strategies such as using combination therapy for the initial treatment of hypertension may be required.

Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs
Lim S et al., (2007) *The Lancet*, Volume 370, Issue 9604, 15–21 December 2007, Pages 2054–2062
http://www.sciencedirect.com/science/article/pii/S0140673607616997

The authors aimed to estimate the number of deaths that could be averted and the financial cost of scaling up, above current coverage levels, a multidrug regimen for prevention of cardiovascular disease (a statin, aspirin, and two blood-pressure-lowering medicines) in 23 LIMCs. Over a 10-year period, scaling up this multidrug regimen could avert 17.9 million deaths from cardiovascular disease (95% uncertainty interval 7.4 million–25.7 million). 56% of deaths averted would be in those younger than 70 years, with more deaths averted in women than in men owing to larger absolute numbers of women at older ages. The 10-year financial cost would be US$ 47 billion (US$ 33 billion–$61 billion) or an average yearly cost per head of US$ 1.08 (US$ 0.75–1.40), ranging from $0.43 to $0·90 across low-income countries and from US$ 0.54 to US$ 2.93 across middle-income countries.

This information provides a basis for developing country-specific agendas for action and investment plans by identifying the additional amount of resources that need to be mobilised. It suggests that in some settings monetary resources are not an insurmountable barrier to scaling up this strategy; low-income countries, however, will clearly need large amounts from external donors. In the Democratic Republic of the Congo, Burma, and Ethiopia, for example, this investment would represent around a tenth or more of current health expenditure.

There are several factors that any investment plan for this strategy should also consider. A key one will be ensuring access and supply of inexpensive cardiovascular medicines. This factor is crucial since drug costs, even at the generic-based median prices reported by MSH, account for two-thirds of the estimated resource needs. At the lowest drug price reported by MSH, the overall financial burden of this strategy could be substantially reduced to US$ 0.56 per person per year. Availability of these multidrug regimens in the public sector, however, is low and, although availability is higher in the private sector, the price is substantially higher than prices reported by MSH and unaffordable for most individuals who need them. A range of policies is required at both international and country levels, such as promoting local manufacturing of generic products, pooling procurements, and price regulation, to ensure availability of inexpensive, high-quality cardiovascular medicines.

The integration of service delivery of multidrug regimens for cardiovascular disease prevention with other ambulatory health services – i.e. an opportunistic screening approach – aims to improve the cost-effectiveness and feasibility of strategies, particularly during the early stages of scaling-up coverage. These benefits need to be balanced against a potential increase in health inequalities. This problem is not unique; for example, the effect of scaling up antiretroviral therapy is receiving increasing attention.

There are several limitations of the current analysis that should be considered. Although the best available data have been used, according to the authors, there is uncertainty, particularly in the least-developed settings where such data are scarce. For example, the estimates of patients' adherence to medication used in this analysis are derived from studies in high-income settings, and these might not be easily transferable to low-income and middle-income country settings. The authors have, however, done extensive uncertainty analysis to quantify a plausible range. They have also not measured potential cost savings of averting cardiovascular disease events that might offset the costs of this intervention, nor have we measured the potential costs of side-effects that might add to the costs of scaling up this intervention.

Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial
China Salt Substitute Study Collaborative Group. (2007). *Journal of hypertension*, 25(10), 2011-2018.
http://www.ncbi.nlm.nih.gov/pubmed/17885542

Dietary sodium and potassium consumption is associated with blood pressure levels. The objective of this study was to define a practical and low-cost method for the control of blood pressure by modification of these dietary cations in rural Chinese.

This study was a double-blind, randomized, controlled trial designed to establish the long-term effects of a reduced-sodium, high-potassium salt substitute (65% sodium chloride, 25% potassium chloride, 10% magnesium sulphate) compared to normal salt (100% sodium chloride) on blood pressure among high-risk individuals. Following a 4-week run-in period on salt substitute, participants were randomly assigned to replace their household salt with either the study salt substitute or normal salt for a 12-month period.

The mean age of the 608 randomized participants was 60 years and 56% of them were female. Sixty-four percent had a history of vascular disease and 61% were taking one or more blood pressure-lowering drugs at entry. Mean baseline blood pressure was 159/93 mmHg (SD 26/14). The mean overall difference in systolic blood pressure between randomized groups was 3.7 mmHg (95% confidence interval 1.6-5.9, P < 0.001). There was strong evidence that the magnitude of this reduction increased over time (P = 0.001) with the maximum net reduction of 5.4 mmHg (2.3-8.5) achieved at 12 months. There were no detectable effects on diastolic blood pressure.

Salt substitution produced a substantial and sustained systolic blood pressure reduction in this population, and should be actively promoted as a low-cost alternate or adjunct to drug therapy for people consuming significant quantities of salt.

4. Cancer prevention and early detection

Cervical Cancer Prevention in Low- and Middle-Income Countries: Feasible, Affordable, Essential
Sahasrabuddhe VV, Parham GP, Mwanahamuntu MH, & Vermund SH (2012). *Cancer Prevention Research*, 5(1), 11-17.
http://cancerpreventionresearch.aacrjournals.org/content/5/1/11.abstract?ijkey=4831ab53a272095e116eee13334a246734013a75&keytype2=tf_ipsecsha

The continued high incidence of cervical cancer across LMICs has prompted the development, evaluation, and adoption of innovative approaches for improving sustainable prevention efforts. Visual inspection with acetic acid (VIA) is readily mastered by nonphysician providers and has been extensively studied as an alternative screening approach to the Pap smear. VIA gives immediate results and can be linked to cryotherapy in a relatively low-cost single-visit "see-and-treat" approach.

According to the authors, visualization of lesions is not the only screening alternative to Pap smears. Human papillomavirus (HPV) can be detected in cervical sampling by conducting a pelvic examination or through patient self-collection. HPV testing offers the most biologically compelling method of screening because virtually all cervical cancers result from chronic, persistent HPV infection. In comparison with other screening methods, HPV screening was superior in helping reduce both the incidence and mortality of cervical cancer in a large community-based randomized trial. With the ongoing development of low-cost, rapid molecular-assay technologies for HPV that are robust for field operations, HPV-based screening has the promise to become a frontline method for cervical cancer screening, to maximize detection and expand access across LMICs. Integrating HPV testing with VIA-based "see-and-treat-or-refer" platforms can combine the high accuracy of HPV DNA testing with the same-visit benefit of triage by VIA-based screening. With innovative public–private partnerships, it can be expected that HPV screening tests would be cheap enough for widespread deployment in low-income nations.

Vertical programs, such as HIV screening, also should be broadened to include cancer screening. Although immunosuppressed women are of special concern, mitigation of risk through pragmatic clinical prevention services, including HPV vaccine, can be expanded to reach a wider group of at-risk women in an implementation catchment area.

Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries
Chalkidou K, Marquez P, Dhillon PK, Teerawattananon Y, Anothaisintawee T, Gadelha CAG, & Sullivan R. (2014). *The Lancet Oncology*, 15(3), e119-e131.
http://www.sciencedirect.com/science/article/pii/S1470204513705473

A key problem in cervical cancer screening in Sub-Saharan Africa is the limited health-system capacity to undertake widespread cytological screening. Of 20 countries reporting cervical cancer screening activities in 2009 in Africa, only 11 had ongoing country programmes; of 49 projects initiated, only six were funded by the domestic government.

Demonstration programmes in Botswana and Zambia show how low-cost see-and-treat procedures (i.e. immediate treatment after assessment or diagnosis) when adopted and

integrated into existing service delivery platforms – such as maternal and child health or HIV/AIDS programmes – can serve as equally effective alternatives to conventional diagnosis and management approaches, particularly for reaching women living in distant or underserved regions.

In view of the present high cost of HPV vaccines, countries need to use available evidence to decide the best strategies for their use to allocate resources efficiently and equitably. Although the Gavi Alliance (http://www.gavi.org/) has decided to support the introduction of HPV vaccines, and public-private partnerships exist to make breast and cervical screening and HPV vaccination more available and affordable in Sub-Saharan Africa, countries still need to consider the longer term budgetary implications for sustainable programmes, and they must ensure that effective treatment is available for detected malignant lesions.

Cancer screening and prevention in low-resource settings
Shastri A, & Shastri SS. (2014). *Nature Reviews Cancer* (14), 822–829.
http://www.nature.com/nrc/journal/v14/n12/full/nrc3859.html

Evidence on effectiveness of taxation and smoke-free laws for tobacco control is cited for high-income countries. This article notes reports of strong population-based tobacco control interventions from India, namely the Smokefree Mumbai Campaign and the Thai tobacco cessation programme involving pharmacists.

The Smokefree Mumbai Campaign, launched in March 2009, is led by Action Council Against Tobacco and the Public Health Department of the Municipal Corporation of Greater Mumbai. The goal of this campaign is to reduce exposure to second-hand smoke in Mumbai, India, by ensuring strict implementation of the national law for smoke-free public and work places. The key activities of the campaign are political and community assessment, sensitization and awareness of the citizens, key stakeholders and policy makers, grassroots mobilization, media advocacy, support of the enforcement agencies in monitoring and implementation of the law, research and evaluation.

The campaign uses innovative strategies such as public messaging through religious festivals, social media messaging and counselling of restaurant and transport workers union leaders very effectively. One of the important achievements of this campaign was to argue favourably in the Mumbai High Court that elements of the national tobacco control law be included in the licensing terms and conditions for restaurants in Mumbai. This resulted not only in strict enforcement but also very high compliance, as repeated offenders were liable to lose their operating licenses as per the new licensing conditions. The Smokefree Mumbai Campaign has resulted in substantial reduction of exposure to second-hand smoke in public and work places in Mumbai. Other cities in India are now using the same strategies to convert their cities into smoke-free cities.
(See www.smokefreemumbai.org)

Model-Based Impact and Cost-Effectiveness of Cervical Cancer Prevention in Sub-Saharan Africa
Kim JJ, Campos NG, O'Shea M, Diaz M, & Mutyaba I. (2013). *Vaccine*, 31, F60-F72.
http://www.sciencedirect.com/science/article/pii/S0264410X13005197

Using population and epidemiologic data for 48 countries in Sub-Saharan Africa, the authors used a model-based approach to estimate cervical cancer cases and deaths averted, disability-adjusted life years (DALYs) averted and incremental cost-effectiveness ratios (I$ (international dollar) per DALY averted) for human papillomavirus (HPV) vaccination of pre-adolescent girls.

There were large variations in health benefits across countries attributable to differential cancer rates, population size, and population age structure. More than half of DALYs averted in Sub-Saharan Africa were in Nigeria, Tanzania, Uganda, the Democratic Republic of the Congo, Ethiopia, and Mozambique. When the cost per vaccinated girl was I$ 5 (I$ 0.55 per dose), HPV vaccination was cost-saving in 38 Sub-Saharan African countries, and cost I$ 300 per DALY averted or less in the remaining countries. At this vaccine price, pre-adolescent HPV vaccination followed by screening three times per lifetime in adulthood cost I$ 300 per year of life saved (YLS) in Uganda (per capita GDP I$ 1,140) and I$ 1,000 per YLS in South Africa (per capita GDP I$ 9,480). In nearly all countries assessed, HPV vaccination of pre-adolescent girls could be very cost-effective if the cost per vaccinated girl is less than I$ 25-I$ 50, reflecting a vaccine price being offered to the Gavi Alliance (http://www.gavi.org/). In-country decision makers will need to consider many other factors, such as affordability, acceptability, feasibility, and competing health priorities, when making decisions about cervical cancer prevention.

Introducing HPV vaccine in developing countries—key challenges and issues
Agosti JM, & Goldie SJ. (2007). *New England Journal of Medicine*, 356(19), 1908-1910.
http://www.nejm.org/doi/full/10.1056/NEJMp078053

A new quadrivalent human papillomavirus (HPV) vaccine has now been proved to be effective in preventing cervical intraepithelial neoplasia grade 2 and grade 3 caused by HPV types 16 and 18. According to meta-analyses, these two types of HPV account for 65 to 72% of all cervical cancers in less developed regions (65 to 72%).

An analysis of options for cervical-cancer control in Brazil found that at a cost of $5 per dose (excluding wastage, administration, and costs of programs), the cost-effectiveness ratio associated with adolescent vaccination would be less than $150 per year of life saved, and vaccination combined with screening women three times during their lifetime would meet the criteria for a very cost-effective intervention.

Research on cancer prevention, detection and management in low- and medium-income countries
Sankaranarayanan R, & Boffetta P. (2010). *Annals of oncology*, 21(10), 1935-1943.
http://annonc.oxfordjournals.org/content/21/10/1935.full#ref-18

During the last decades, several causes of cancer which are of particular relevance to LMICs have been identified through epidemiological and clinical studies. Examples include aflatoxins and hepatitis B virus (HBV) for liver cancer, Schistosoma haematobium infection for bladder cancer, and liver flukes for cholangiocarcinoma. In addition, the etiological role of human papillomavirus (HPV) in cervical and other cancers and that of Helicobacter pylori in stomach cancer are of particular importance in LMIC because of the high incidence of these cancers and the high prevalence of the infections. These discoveries have resulted in major opportunities for primary prevention, including vaccination against HBV and HPV, treatment of H. pylori infection and improvement in food storage aimed at reducing aflatoxin contamination.

HPV testing has clearly a higher sensitivity (pooled sensitivity 90%) but somewhat lower specificity (pooled specificity 88%) than cytology. However, it is limited by its current costs, cumbersome procedure and equipment, and there are efforts to develop inexpensive, rapid yet accurate HPV test formats and tests on the basis of E6 and E7 viral oncogenes to improve specificity and the need for repeat HPV DNA testing. In LMICs, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease. However, the currently available HPV tests are expensive and cumbersome

and there is a need to develop simple, affordable, safe, accurate, reliable, rapid, portable and acceptable biochemical tests for use in low-resource settings.

Translating the vast potential of HPV vaccination into public health practice is currently limited by high costs, uncertain long-term protection and cross-protection against other HPV types, acceptability issues, information needs, health system capacity and delivery logistics to vaccinate preadolescents and adolescents.

Prevention of occupational cancer has been implemented with relative success in HIC during the second half of the 20th century. About 30 occupational exposures have been recognized to cause cancer in exposed workers; very limited information is available from LMIC on patterns of exposure to occupational carcinogens and cancers that can be attributed to workplace carcinogenic exposures.

Human papillomavirus vaccine support
Gavi Alliance (Web page accessed 16/7/15)
http://www.gavi.org/support/nvs/human-papillomavirus-vaccine-support/

A record low price for HPV vaccines has opened the door for poor countries to vaccinate millions of girls against a devastating women's cancer.

The Vaccine Alliance are assisting the poorest countries with access to a sustainable supply of HPV vaccines for as low as US$ 4.50 per dose.

For HPV demonstration programmes, Gavi will cover the full cost of HPV vaccines. However, countries introducing HPV vaccine nationally are required to meet the standard co-financing commitment.

The high cost of the vaccine and challenges of immunising girls aged 9 to 13 years have been barriers to introduction of the vaccine in poorer countries. Gavi is working to bridge the equity gap by providing the vaccine at affordable and sustainable prices, and to support countries with demonstration projects in order to build capacity and infrastructure to deliver the vaccines.

Since Gavi began providing support for HPV vaccines in 2013, over 20 countries have been approved to introduce the vaccines – the large majority will be HPV demonstration projects. This will allow them to test the best ways to deliver HPV vaccines to girls. These demonstration projects will pave the way for countries to build the capacity and infrastructure needed to vaccinate girls nationwide. Rwanda will introduce HPV vaccine nationally. By 2020, it is estimated that over 30 million girls in more than 40 countries will be vaccinated against HPV.

Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review
Fesenfeld M, Hutubessy R, & Jit M. (2013). *Vaccine*, 31(37), 3786-3804.
http://www.ncbi.nlm.nih.gov/pubmed/23830973

The World Health Organization recommends establishing that human papillomavirus vaccination is cost-effective before vaccine introduction. The authors searched Pubmed, Embase and the Cochrane Library to 1 April 2012 for economic evaluations of human papillomavirus vaccination in low and middle income countries. The authors found 25 articles, but almost all low income countries and many middle income countries lacked country-specific studies. Methods, assumptions and consequently results varied widely, even for studies conducted for the same country. Despite the heterogeneity, most studies conclude

that vaccination is likely to be cost-effective and possibly even cost saving, particularly in settings without organized cervical screening programmes. However, study uncertainty could be reduced by clarity about vaccine prices and vaccine delivery costs. The review supports extending vaccination to low income settings where vaccine prices are competitive, donor funding is available, cervical cancer burden is high and screening options are limited.

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6. Additional information

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