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## Invited Commentary

Lancet Global Health on UHC and chronic medication

## Title page

### Universal health coverage and chronic conditions

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## Commentary

The upcoming UN high-level meeting on universal health coverage in September provides a developmental framework for international and national agendas on the universal prevention and treatment packages and financial protection, worldwide. [1, 2] Universal coverage of prevention and treatment of chronic diseases is a very relevant topic area given the globally rising non-communicable disease epidemics in the world's ageing populations.[3-8] In addition, there is increasing recognition of the late chronic consequences of major infections exemplified by post-TB lung damage, metabolic consequences in HIV, neuropathologies from meningitis and malaria, and chronic morbidity from neglected tropical diseases, like in lymphatic filariasis. These developments demand a shifts towards the development and stepped-up provision of new and integrated models of chronic care provision, especially in low- and middle-income settings. [7] Positive evidence for fixed-dose treatment combinations (FDCs) is accumulating, along with affordable strategies to improved access to, and use of, effective medical prevention and treatment, especially in chronic conditions. [4-6, 9-13] FDCs have important advantages for patients and health systems, including simpler dose schedules, decreased pill burden, reduced stockouts, easier task sharing, training, and supervision, resulting in promoting large-scale access, acceptance, and production, such as reported in this issue and as also seen in HIV and TB control. [9, 10]

Lung et al. [10] report the attractiveness in both health benefits and economic terms of triple fix-dose combinations (FDCs) in the treatment of high blood pressure, combining amlodipine, telmisartan and chlorthalidone. FDCs, which combine two or more BP lowering drugs that are commonly taken together into a single pill, have been proven to improve patients' adherence to medication regimens and BP control rates in a Sri Lankan trial, while their scenarios show the attractiveness in terms of health care costs and life years gained and disability prevented.

Consequently, in an unusually rapid reaction, the World Health Organization has recently added FDCs of blood pressure lowering drugs to its Essential Medicines List, supported by relevant societal and professional organisations. It is a shining example of international co-ordination and collaboration. Adding the combination of BP lowering drugs to the list is essential to improve the availability and affordability of these drugs. It promotes access for over 1 billion people with high BP worldwide to regularly take medication to prevent strokes and myocardial infarctions resulting in mid-aged disability and premature death.[14]

Inevitably, the economic study by Lung et al. [10] is based on limited empirical observations and during only two years while the differences with control cases show a plateau after six weeks. Their TRIUMPH trial cannot be considered as a pure ‘efficacy’ trial. In real-life settings as it the case one can expect short-term compliance and Hawthorne effects, while in the long-term economic evaluation changes in long-term behaviour and compliance are important. [10] In addition, non-linearity of the risk functions, depending on absolute BP levels, age, and selective survival effects may result in huge differences in outcomes between sub-populations.

Li et al.[9] take the FDCs one step further and show the potential health effect and cost reductions of the large-scale introduction of FDCs including aspirin, lisinopril, atenolol, and simvastatin to address multiple risk factors,. Their careful and well-documented model-based economic analyses one more attempt to assess the options for secondary CVD risk prevention in large country populations across the world. They recommend a large-scale introduction of this 'polypill' for secondary prevention. There is one caveat: aspirin in primary CVD prevention was recently shown to be ineffective [15]). Secondary prevention in polypill trials show improvements in proxy outcomes, but not in mortality outcomes, possibly due to lack of sample size / follow-up duration. Primary and secondary CVD prevention has been addressed as early as Murray [12], including the potential benefits of polypill combinations. [8]

Other treatment combinations are already in use in the treatment of chronic conditions including lung health [3, 4, 6], diabetes ([5], HIV and tuberculosis [7, 11]. In lung health there is the question if a simple strategy of using a combined corticosteroid/rapid-onset long-acting  $\beta_2$  agonist (ICS/LABA) inhaler ‘as required’ or, if clinically indicated, ‘both as required, and regularly’ reduce asthma exacerbations in children and adults LMIC settings, with a possible potential role in the management of post-TB chronic lung disease. [4, 6]. .

Rigorous epidemiological and economic evaluation of FDCs is complex: mono-therapeutic strategies, in many cases, are the norm and widely accepted in health guidelines and in clinical practise. Both limited effectiveness information and ethical boundaries in the identification of control groups make the use of mathematical modelling unavoidable. [16, 17] In a state-of-the-art approach, Li et al.[9] use estimates from the PURE study, including compliance, as a control. They use the proxy outcomes of a single LMIC trial and the aggregated compliance data from two HIC trials, calibrated against recent BOD estimates.

They optimistically include the health effects of the four individual drugs secondary event prevention among post-first-event patients. These combined, multiplicative, indeed proxy effects of their 'polypill' are simulated in scenarios to estimate the potential population benefits. It is realistic to weight the benefits against both the health care cost based on international generic pricing and local commercial pricing. However, the assumed potential cost-offsets from preventing secondary events will be low, in many resource-limited settings. Hopefully, in the near future monitoring the implementation of up-scaling efforts will teach us on the real-life effectiveness of these FDCs.

Findings from economic evaluations - cost-effectiveness estimates – often stimulate debates on what level of outcomes is economically attractive. The WHO CHOICE programme has modified its position substantially [16], following the 2<sup>nd</sup> Panel on Cost-effectiveness. They conclude that there is no absolute (WHO) cost-effectiveness threshold and individual countries should define their own approach [17]. The UK, through the threshold of £20,000 per healthy year gained set by NICE, is the only country that applies an absolute standard in decision making on package formulations. The best approach globally is to respect national governmental decision-making that can take into account country standards and the country overall situation and the particulars of the health system.[16-19] It is striking that Lung's group of clinical authors is based in California, with few members from India, Mexico, and Nigeria, and none from China. This calls into question their ability to address affordability, national opportunity costs (total budget impact), feasibility, and generalisability at country and sub-country levels. One would like to see an earlier involvement of funding bodies, both internationally and nationally.

Real life policy making in low-income settings is complex and will increase in complexity as more and more options become available to deal with the health burden of chronic conditions. Although cost-effective, the overall national budget impacts, especially in the larger countries, of most new intervention packages can nevertheless be huge, as the number of people with chronic conditions is ever increasing. Assuming concurrent retail market pharmaceutical prices, these budgets may be at 10% of the per capita GDP. These are huge budgets in large economies. Would Ministries of Health and Finance or national cabinets prefer to use this money in a different way in health or otherwise? Inevitably, the ongoing equity debates in allocation of country resources have been part of national decision making for decades, especially in the case of LMICs. It is striking, that the UN SDGs leading theme

is the inequalities between population sub-groups, including gender, the poor, the disabled, and minorities but also the huge inequalities between countries. These equity questions have not been clearly addressed in the two studies, nor in most other recent evaluations. Certainly, from now on, progressive realisation i.e. the promotion of equity in universal access and coverage will be higher on the agenda, given proven effectiveness and efficiency of new interventions and strategies. [1, 2, 18-20]

Existing recommendations in relation to the upcoming high-level UN meeting focus on political leadership beyond health, to exclude leave no one behind, to regulate and legislate, internationally and nationally the upcoming UHC efforts, while upholding quality of (chronic) care [1]. Universal coverage of prevention and treatment of chronic conditions will have to be a substantial part of this process, while at the same time reducing inequalities in financing, access and utilization, in between countries and within countries. [18-20]

Conflicts of interests: none.

## References

1. UN. *Moving together to make the world a healthier place*. [www] 2019 [cited 2019 15/08/2019]; Available from: <https://www.un.org/pga/73/event/universal-health-coverage/>.
2. UNSD, U.N.-. *Sustainability Development Goals Report Annual reports 2019*; Available from: <https://unstats.un.org/sdgs/report/2019/The-Sustainable-Development-Goals-Report-2019.pdf>.
3. Babar, Z.U., et al., *The availability, pricing and affordability of three essential asthma medicines in 52 LMICs*. *Pharmacoeconomics*, 2013. **31**(11): p. 1063-82.
4. Bateman, E.D., et al., *As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma*. *N Engl J Med*, 2018. **378**(20): p. 1877-1887.
5. Bazargani, Y.T., et al., *Selection of essential medicines for diabetes in low and middle income countries: a survey of 32 national essential medicines lists*. *PLoS One*, 2014. **9**(9): p. e106072.
6. Beasley, R., J. Fingleton, and M. Weatherall, *Restriction of LABA use to combination ICS/LABA inhaler therapy in asthma*. *Thorax*, 2013. **68**(2): p. 119-20.
7. Garrib, A., et al., *Integrated care for human immunodeficiency virus, diabetes and hypertension in Africa*. *Trans R Soc Trop Med Hyg*, 2018.
8. Niessen, L.W., et al., *Tackling socioeconomic inequalities and non-communicable diseases in low-income and middle-income countries under the Sustainable Development agenda*. *Lancet*, 2018. **391**(10134): p. 2036-2046.
9. Lin, J.K., et al., *Cost-Effectiveness of a Fixed-Dose Combination Pill for Secondary Prevention of Cardiovascular Disease in China, India, Mexico, Nigeria, and South Africa*. *Lancet Glob Health*, 2019.
10. Lung, T., et al., *Fixed low-dose triple combination antihypertensive medication versus usual care in patients with mild to moderate hypertension in Sri Lanka: A within-trial and modelled economic evaluation of the TRIUMPH trial*. *Lancet Glob Health*, 2019.
11. Hwang, T.J. and S. Keshavjee, *Global financing and long-term technical assistance for multidrug-resistant tuberculosis: scaling up access to treatment*. *PLoS Med*, 2014. **11**(9): p. e1001738.
12. Murray, C.J., et al., *Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk*. *Lancet*, 2003. **361**(9359): p. 717-25.
13. Gallardo, C.R., et al., *Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis*. *Cochrane Database Syst Rev*, 2016(5): p. Cd009913.
14. WHO. *Fixed-dose combination antihypertensives Selection and Use Essential Medicines 2019* [cited 2019; Available from: [https://www.who.int/selection\\_medicines/committees/expert/22/selected\\_medicines/essential\\_medicines/en/](https://www.who.int/selection_medicines/committees/expert/22/selected_medicines/essential_medicines/2019/selected_medicines/essential_medicines/en/)].
15. McNeil, J.J., et al., *Effect of Aspirin on Disability-free Survival in the Healthy Elderly*. *N Engl J Med*, 2018. **379**(16): p. 1499-1508.
16. Bertram, M.Y., et al., *Cost-effectiveness thresholds: pros and cons*. *Bull World Health Organ*, 2016. **94**(12): p. 925-930.
17. Sanders, G.D., et al., *Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine*. *Jama*, 2016. **316**(10): p. 1093-103.
18. Baltussen, R., et al., *Progressive realisation of universal health coverage: what are the required processes and evidence?* *BMJ Glob Health*, 2017. **2**(3): p. e000342.
19. Baltussen, R. and L. Niessen, *Priority setting of health interventions: the need for multi-criteria decision analysis*. *Cost Eff Resour Alloc*, 2006. **4**: p. 14.
20. The Lancet, *Prioritising disability in universal health coverage*. *Lancet*, 2019. **394**: p. 187.



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