OPEN LETTER

A novel initiative to improve access to medicines for control of non-communicable diseases in low- and middle-income countries [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

The global burden of non-communicable diseases (NCDs) is growing, and access to prevention and treatment strategies remain limited, especially for those in low- and middle-income countries (LMICs).

Novel approaches are needed to improve access and affordability of medicines that can treat NCDs in LMICs. The Access and Affordability Initiative (AAI) is a public private partnership aiming to improve access to and availability of essential medicines for the treatment of NCDs and strengthening of health systems. Through this novel initiative a prospective cohort of patients with hypertension and diabetes were followed in Ghana and the Philippines to examine the effect of differential pricing on access to treatment of hypertension and diabetes. An integrated approach including differential pricing, health systems strengthening, improved supply chain management and greater affordability can improve access to medicines for NCDs.

While differential pricing has several advantages for improving the affordability of NCD medicines in LMICs, it can't overcome all barriers as a standalone approach. An integrated approach to health systems strengthening, supply chain management and affordability are needed to overcome key challenges in getting medicines for NCD to patients in LMICs. Availability and affordability of medicines to treat NCDs among vulnerable patients will help achieve Universal Health Coverage (UHC).
Keywords
Hypertension, Diabetes, Ghana, Differential Pricing, LMIC, Non-Communicable Diseases, Universal Health Coverage

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Amendments from Version 1

In this revised version, the manuscript provides a more detailed description of the AAI, and how the AAI has tackled the issue of access through diverse strategies. In addition, the introduction has been shortened, focusing on why NCDs matter, as suggested by both reviewers. We then describe the AAI as a potential solution to tackling the issue of access to NCD treatment. As the protocol has previously been published, instead of providing more details on the methodology of the AAI, we refer to the published protocol (which describes how the EML was chosen, which variables were studied, which health system strengthening interventions were implemented, etc.). We better define access, referring to the WHO/MSG definition, as well as one described by Jacobs et al. We also provided some of the results of the study and why it is important that access to NCD treatment is critical. We also refer to the experience the HIV epidemic has with differential pricing, while citing some of the challenges encountered by both NCDs and HIV. Finally, we cite the importance of political advocacy, again referring to the HIV experience in improving access and affordability. We also stress that differential pricing alone is NOT a solution, as health systems strengthening is also critical in improving NCD outcomes.

Any further responses from the reviewers can be found at the end of the article.

Introduction

Burden of non-communicable diseases

Non-communicable diseases (NCDs), especially cardiovascular diseases, diabetes, and cancer, have emerged as the leading cause of premature deaths globally. Eighty-six per cent of these deaths are estimated to occur in low-and middle-income countries (LMIC), where they pose a serious public health threat. There is evidence that shows that more than 9 million of all deaths attributed to non-communicable diseases (NCDs) occur before the age of 60. Of these “premature” deaths, 90% occurred in low- and middle-income countries.

Access and affordability of medicines for NCDs in LMICs

For many patients, the high cost of medicines constitutes a major barrier to access innovative patented medicines, but also to the World Health Organization (WHO) list of essential medicines, 92% of which are off-patent. As the prevention and control of NCDs often requires life-long treatments, novel initiatives, which improve access and affordability, are needed. Health financing reforms and enhanced normative guidance are required for current financing strategies, such as health insurance (with or without co-payment), out-of-pocket expenditure, financing pools and pre-payment, in order to enhance patient access to medicines and overall health outcomes. Essential medicines used to treat NCDs tend to have limited availability and affordability, especially in public sector settings in LMICs, thus negatively impacting control of NCDs. Approximately 90% of individuals in LMICs are estimated to use their own funds to purchase medicines, resulting in out-of-pocket expenditures for medicines being the highest expenditure after food, resulting in challenges with affordability, posing major burdens on government budgets. A significant proportion of morbidity and mortality due to NCDs can be prevented if medicines are made accessible and affordable.

The lack of available data on pharmaceutical expenditure, specifically on the types of medicines procured or sold, public and private sector spending, and the degree of access by key population subgroups was recently highlighted by an article in the Lancet. It recommended that Governments and health systems create and maintain information systems for routine monitoring of data bearing on the affordability of essential medicines, as well as price and availability, in the public and private sectors. The aim of this paper is to discuss differential pricing for the treatment of NCDs, as a financing scheme to help achieve Universal Health Care.

Study: Access and Affordability Initiative

The Access and Affordability Initiative (AAI) is a multilateral collaboration between multiple stakeholders with the aim of improving access to and availability of essential medicines for the treatment of NCDs and strengthening of health systems. It brings together four major biopharmaceutical companies – Merck, Sharp and Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A., Novartis, Pfizer and Sanofi – and the Bill & Melinda Gates Foundation, who have initiated a public private partnership with the Ministries of Health in Ghana and the Philippines. AAI is one of the initiatives supporting Access Accelerated, a global partnership of a coalition of biopharmaceutical companies to address the barriers to access for NCDs in LMICs. Access Accelerated was launched at the World Economic Forum’s Annual Meeting in Davos by twenty-two leading biopharmaceutical companies to advance access to NCD prevention and care in low and lower-middle income countries.

Through this novel initiative a prospective cohort of patients with hypertension and diabetes were followed in Ghana and the Philippines at multiple sites, allowing these countries, with the support of the Ministry of Health, as well as academic institutions, to study the effect of within-country differential pricing and health systems strengthening on several outcomes, including disease control, complications of diabetes and hypertension, as well as adherence. Health system strengthening activities included the development of clinical guidelines, training on supply chain and clinical management, education, counseling and strengthening of supply chain management. A detailed protocol of the GAAP study has been published elsewhere. The essential medicines list (EML) that was supported by GAAP included medicines that are not included in National Health Insurance Scheme (NHIS). The NHIS Medicine List is generally based on the Essential Medicine List (EML) promulgated by the Ministry of Health and comprises a list of minimum medicine needs for a basic health-care system. However, preliminary unpublished data from an institutional appraisal performed at six pilot sites identified the following barriers to access to safe and effective medicines for the management of hypertension and diabetes: (a) inability of low- and middle-income patients to afford out of pocket medicines that are not on the NHIS; (b) medicine shortages or stock-outs, and (c) lack of availability of medicines preferred by prescribers. Therefore, alternative strategies that could supplement the NHIS would be crucial in addressing the limited range of
medications on the NHIS Medicine List, as well as reducing the cost of out-of-pocket payments for non-insured medicines.

The initiative has provided a unique opportunity to examine whether differential pricing can improve access to affordable medicines in the developing world. Access has previously been defined by the Access to Medicine Framework (ATM) using the 4As, including ‘Availability’, ‘Accessibility’, ‘Acceptability’ and ‘Affordability’, with ‘Quality’ of products and services as a cross-cutting determinant. We define access from a health system’s perspective, rather than from a vertical framework (focused on supply), as described by Jacobs et al.9.

Though the study demonstrated that it is important that in order for differential pricing to be effective among low-income patients, it is critical to achieve a substantial price reduction to reflect equity and affordability.

The AAI has been able to demonstrate predictors for uncontrolled hypertension (care tertiary longer duration of hypertension diagnosis, poor adherence to therapy, reported difficulties in obtaining antihypertensive medications and number of antihypertensive medications prescribed) and uncontrolled diabetes (duration of diabetes diagnosis, absence of a health insurance scheme, the number of diabetes medicines). Through the AAI, control of both hypertension and diabetes improved with study interventions (increased frequency of follow-up, training of health care providers, improved supply chain, etc.)10,11.

Differential Pricing and Health Systems Strengthening

Differential pricing, an approach used to price medicines based on the purchasing power of payers in different socioeconomic segments, within countries or between countries, has been shown to be beneficial and lead to improvement of access and affordability.11,12.

Thus far, the use of differential pricing has generally been limited to vaccines, contraceptives, antimalarials and antiretrovirals in the context of the Global Fund and Global Alliance for Vaccine Initiative, where price reductions were achieved through such strategies as high-volume purchasing, reliable and adequate financing, public advocacy, negotiation, and market competition. Some of the challenges in the roll out of differential pricing stand out, as this approach doesn’t completely address non-price barriers to access, such as challenges related to regulation and weak supply chain and health systems. With regards to supply chain challenges, frequent stockouts, inability to forecast accurately, inefficient distribution systems, or leakage of medicines for private resale, can all impact access.13.

Therefore in order to improve access and affordability using differential pricing as a financing scheme, it is important that an integrated approach be utilized which includes robust partnerships between multiple stakeholders (governments, donors, biopharmaceutical companies, UN agencies, non-governmental organizations), as well as targeted efforts to strengthen supply chain and health systems. Health systems strengthening efforts should focus on improved information management systems, supply chain, capacity building of trained staff, etc.

As is the case with NCDS, HIV requires life-long treatment and ARVs are expensive. In 2000, the Accelerating Access Initiative first launched a differential pricing strategy for anti-retrovirals (ARVs)14. There are several lessons that can be learned from the HIV experience. First, differential pricing alone was not sufficient to lower the price of ARVs, as large-scale financing of HIV/AIDS treatment and the development of generic ARV markets started to become more prominent. Waning et al. also found that differential pricing for several ARVs were 23-498% higher than generic prices.14,17

Our study demonstrated that differential pricing needs to be coupled with health systems strengthening in order to improve disease control. Reduction of out-of-pocket expenditure can also be achieved through co-payments (in countries with existing health insurance). Access to treatment alone is not sufficient, but rather education, counseling, improved supply chain and training of health care providers are all needed to improve disease control.

Differential pricing alone as a scheme does not lead to equity or affordability, as it primarily ensures that different prices are charged to different segments of the market for the same product, therefore focusing on the producer’s perspective. Additional evidence will be needed to determine the generalizability of such an intervention in other LMIC to tackle the issue of access to treatment.

The AAI study has provided essential data on access to medicines, affordability of treatment, clinical outcomes, as well as out-of-pocket expenditure by rural and urban populations in both Ghana and the Philippines. This information system will be shared with the respective Ministries of Health in both countries and will assist in providing important policy recommendations to these respective Ministries.

Universal Health Coverage

Differential pricing is an instrument among many to increase affordability of medicines, which can contribute to UHC through reduced expenditure and greater access to medicines. Beneficiaries may still need to pay out-of-pocket, requiring co-payments, suggesting that the coverage component might not be completely addressed through differential pricing.

UHC is defined as the ability to access quality, needed health services, while ensuring that the use of these services does not expose the user to financial hardship. UHC is now a Sustainable Development Goal (SDG) goal: “Achieve UHC, including financial risk protection, access to quality essential health care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.” The concept of UHC ensures a “system-wide effective coverage combined with universal financial protection,” thus avoiding exorbitant out-of-pocket costs. Out-of-pocket financing for chronic
disorders poses a real barrier to increasing access to medicines for poor populations\(^8\).

Given the growing cost to the health system of poorly managed NCDs and of the limited availability of financial resources, targeted, cost-effective interventions are needed. Additional evidence will be required to examine the ability to implement differential pricing as a means to improve access to and affordability of medicines for the treatment of NCDs in a variety of contexts. “To explore viable health financing mechanisms and innovative economic tools supported by evidence” is a policy recommendation in the updated WHO Global Action Plan for the Prevention and Control of NCDs\(^9\).

The AAI presents one example of such an exploration through differential pricing of innovative medicines for the control of NCDs, coupled with health systems strengthening and may reveal an innovative means to improve access to critically needed medicines and thereby help curb the disturbing trends of excess morbidity and mortality from NCDs in LMICs. However, in order to ensure that access to treatment for NCDs becomes a global priority, increased political advocacy is required to ensure that medicines to treat NCDs become more affordable, as was the case with HIV\(^11\).

**Disclaimer**

The views expressed in this article are those of the authors. Publication in Gates Open Research does not imply endorsement by the Gates Foundation.

**Data availability**

No data are associated with this article.

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Version 2

Reviewer Report 27 January 2020

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David J. Heller
Arnhold Institute for Global Health, Department of Medicine/Health System Design & Global Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

I have had the pleasure to review the revised article. Although I was unable to directly compare the current text with the prior text. I feel that the current text addresses my prior concerns as well as the other reviewer’s. Specifically:

1. The abstract is more concise and leads with a description of the AAI.

2. The introduction, too, now introduces the AAI more prominently and clearly.

3. The conclusion also details further next steps and implications of the work.

4. Regarding the other reviewer’s comments, the authors have also added details regarding the methods and results. It remains unclear to me whether the authors have fully addressed her request for more information on data collected, but I defer to her review of that issue.

Based on the above, I now feel the paper is scientifically sound and approved for indexing.

Competing Interests: I am a friend and colleague of Dr. Linda Meta Mobula, though we have not formally collaborated on any research to date

Reviewer Expertise: Implementation science approaches to strengthen non-communicable disease care delivery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 May 2018
Alessandra Ferrario  
Department of Population Medicine, Harvard Pilgrim Health Care Institute, Harvard Medical School, Boston, MA, USA

Thank you for giving me the opportunity to review this article describing the Access and Affordability Initiative (AAI), a public-private partnership to improve affordability and availability of medicines for non-communicable diseases (NCD) in Ghana and the Philippines.

I agree with the comments and suggestions made by the first reviewer, particularly those around the need for more details about the initiative and the evaluation methods, to shorten the introduction and provide a concise and critical analysis of the AAI potential impact. I have made some additional suggestions building on these original comments.

Define access and the contribution of the AAI towards improving access to medicines
The initiative is about improving access to medicines so to start with a definition of access and how the AAI is going to be evaluated are needed. You may want to refer to an existing framework for access to medicines and describe which components the AAI aims to address. For example, the 4A framework used by WHO and MSH in 2000 focuses on accessibility, availability, affordability, acceptability, and quality of products and services. Which components does the AAI address, which not?

Differential pricing aims to improve affordability (depending on coverage either for the health system or for the patient) and in this way increase use of medicines. There is a second component in the AAI which aims to address non-financial barriers to access. Issues related to regulation and weak supply chain are mentioned under the differential pricing subchapter. If the AAI has indeed two components, a financial one (differential pricing) and a health system strengthening one (development of clinical guidelines, training on supply chain and clinical management, strengthening of supply chain management), I think the title of this subchapter should be changed to reflect both and in general the article should give equal weight to both components unless one component was dominant in which case this should be specified.

It would be good to provide more details around the health system strengthening (HSS) interventions and how they are expected to improve access to medicines by acting on one or more of its components. How were these HSS intervention chosen among the many areas of the health systems that could have been strengthened to improve access to medicines (e.g. human resources, health information systems)? A bit of background on the issues hampering access to essential medicines for NCDs in the two countries would help and these challenges could then be linked to the chosen HSS interventions.

Literature on differential pricing and medicines selected for differential pricing
p.3 “Differential pricing, an approach used to price medicines based on the purchasing power of payers in different socioeconomic segments, within countries or between countries, has been shown to be beneficial and lead to improvement of access and affordability.”

I would suggest also discuss some of the potential challenges with differential pricing which have been discussed in the literature. For example (non-exhaustive list):
p.4 “The Access and Affordability Initiative (AAI) is a multilateral collaboration between multiple stakeholders with the aim of improving access to and availability of essential medicines for the treatment of NCDs and strengthening of health systems.”

When you talk about ‘essential medicines’ do you mean that the medicines selected for differential pricing in these two countries were chosen from either the WHO model essential medicines list (EML) or the national EML in the two countries? Please explain how the medicines which are the focus of the intervention were chosen, particularly the balance between on-patent and generic medicines. In the beginning you mention that 92% of the WHO essential medicines are off-patent. So if the focus is on improving access to essential medicines, one would expect them to be the target for interventions.

**Data collection**

p. 4 “The AAI study will help provide essential data on access to medicines, affordability of treatment, clinical outcomes, as well as out-of-pocket expenditure by rural and urban populations in both Ghana and the Philippines. This information system will be shared with the respective Ministries of Health in both countries and will assist in providing important policy recommendations to these respective Ministries.”

It would be helpful to know more about what kind of data (i.e. variables) is being collected and how it is being collected (e.g. through existing data collection systems, surveys, etc.). As you rightly mention in the introduction, limited data to study access to medicines is currently available in low- and middle-income countries and to ensure sustainability, data collection systems should be integrated into existing health information systems.

**Results**

According to https://accessaccelerated.org/initiative/access-and-affordability-initiative/ and http://partnerships.ifpma.org/partnership/access-and-affordability-initiative-aai the studies were due to be completed mid-2017. Can you present some results? Please also provide information on the status of the initiative. When did the interventions start, how long will they last, will there be continuous evaluation?

**Minor comments**

You may want to revise the sentence below:

p.3 “Differential pricing is one of the approaches to achieve the goal of Universal Health Care (UHC).”

Differential pricing is an instrument [among many] to increase affordability of medicines, which can contribute to UHC through reduced expenditure and greater access to medicines. [The patient may still need to pay out-of-pocket, the coverage component is not addressed through differential pricing].

p.3 “Through differential pricing, the cost of medicines in populations with limited access in LMICs can become more affordable and, when coupled with needed health system improvements, has the potential to dramatically increase access to medicines for specific conditions among lower income segments of the population.”

Which health system improvements are needed to improve access to medicines?

p.4 “The WHO recently launched the #beatNCDS campaign, which aims to assist countries to achieve nine global voluntary NCD targets to reduce premature deaths from cancers, heart and lung diseases, and diabetes by 25% by 2025. In order to successfully achieve these goals, it is essential that access to medicines be improved by health financing reforms.”

The AAI tries to improve affordability through differential pricing. A health financing reform goes well
beyond. It is about changing the way providers are remunerated, how health services and products are financed, etc. It is not just about pricing. For this reason, I would not conclude with this statement just before introducing the AAI.

p. 4 “Through this novel initiative a prospective cohort of patients with hypertension and diabetes were followed in Ghana and the Philippines at multiple sites, allowing these countries, with the support of the Ministry of Health, as well as academic institutions, to study the effect of within-country differential pricing of innovative medicines and health systems strengthening on access to innovative medicines, clinical outcomes, including disease control, complications and adherence, for diabetes and hypertension.” This is a very long sentence, please break it down.

Please check this sentence: p.4 “Each of the participating companies independently and made decisions involving the AAI.”

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Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Partly

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
David J. Heller
Arnhold Institute for Global Health, Department of Medicine/Health System Design & Global Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

This article is a welcome addition to the under-studied field of non-communicable disease (NCD) policy. It both outlines several solutions to the problem of NCD medication access, and describes an example organization working in this domain. However, I feel the article would benefit from some revisions for clarity - and some additional details - to make its argument more cohesive and stronger. Additionally, the article makes heavy use of passive voice (e.g., "a prospective cohort...were followed in Ghana and the Philippines"), creating a tone that I think undercuts the force of its argument. See details below - I would be happy to review a revised version as well.

Abstract: the authors spend the first 4 of 6 sentences in this paragraph outline the problems the article addresses - only after that introduction does the reader hear about the Access and Affordability Initiative as a solution. Reworking the abstract to start with a summary statement describing the AAI, and the article's thesis about its role, would help focus the reader's attention. For example, the abstract could start with a statement to the effect of "NCDs are a growing problem in LMICs, and there are too few medicines available/accessible there to treat vulnerable patients. Here we describe a novel initiative - the AAI - and argue it can/should be used to tackle this access issue, through diverse strategies such as differential pricing, supply chain management," etc.

Introduction: in my view this section, like the abstract, introduces the problem in more detail than is necessary, but doesn't introduce the solution. Given the article is brief, I would suggest keeping the background to only 2-4 sentences, in one paragraph, outlining why NCD treatments in LMICs matter: a) because NCDs are a leading and rising cause of death *and* disability in LMIC (would cite references for both); b) many of these deaths are premature and preventable; c) many occur in the lowest-income persons in LMICs (would cite refs for this, such as DiCesare et al, Lancet 2013, or Vellakkal et al, Plos One 2013) and d) the medicines to treat NCDs are often absent. Then, the section can describe the AAI (as is currently listed under "Study" on page 2) as an answer to these problems. As appropriate, the authors could then describe in 1-2 sentences how the AAI addresses (or does not yet address) the main components of medication access in the body of the paper: differential pricing, health system strengthening, etc.

In the body of the paper, I think the reader would benefit from hearing about AAI in more detail than is currently provided. For example, how exactly does AAI support Access Accelerated? Who precisely are the cohort with hypertension/diabetes AAI is following in Ghana and the Philippines? How will the authors measure AAI's impact on the supply chain, medication prices, etc.?

After detailing the AAI's approach, the authors could then transition to all the potential benefits of AAI in more detail: for example, explaining how differential pricing improved access to antiretrovirals for HIV (perhaps providing more details on its precise impact if available), then discussing how AAI is trying to achieve this goal. The authors could also provide details on other strategies to boost medication access in turn, such as tackling supply chain barriers (see work by Prashant Yadav for example); political advocacy...
in support of NCD medication access (see Sandeep Kishore's work for example); and then outline how AAI may or may not help promote NCD medication access along those lines.

**Conclusion:** the article could finish with next steps for how the NCD community can leverage/build on/expand AAI - based on what it does or does not achieve in the domains above - to address any of the above avenues that AAI doesn't yet cover. This approach would help the reader see how their own work can bolster the work AAI is currently doing.

In summary, I think the article is a promising letter that highlights a potentially important new initiative for an under-studied problem. However, with a tighter introduction; more details on the AAI concept; and a more concise analysis of AAI's potential for impact, it could be far more impactful. I thank the journal for the opportunity to review this piece.

**Is the rationale for the Open Letter provided in sufficient detail?**
Yes

**Does the article adequately reference differing views and opinions?**
Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**
Yes

**Is the Open Letter written in accessible language?**
Partly

**Where applicable, are recommendations and next steps explained clearly for others to follow?**
Partly

**Competing Interests:** I am a friend and colleague of Dr. Linda Meta Mobula, though we have not formally collaborated on any research to date.

**Reviewer Expertise:** Implementation science approaches to strengthen non-communicable disease care delivery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.