Chapter 11

Modelling and Economic Evaluation to Inform WHO HIV Treatment Guidelines

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Abstract

International organizations influence national-level health sector priorities by affecting how much funding is available for health care delivery within countries and how that funding is used. The setting of guidelines for the management of diseases (e.g. for malaria, child health, nutrition) by the World Health Organization (WHO) exerts particular influence. Guidelines typically provide syntheses of evidence on clinical efficacy and effectiveness and make recommendations for health care best practice. However, for the most part, they do not well inform the allocation of limited available health care resources. Consequentially, they risk encouraging national and international decision-makers to divert resources away from areas of greater potential gains in population health. In this case study, we reflect upon efforts to incorporate economic evidence into the development of the WHO HIV Treatment Guidelines. We describe how the WHO has incorporated economic insight into these and other guidelines. However, even in this case, the processes currently followed for guideline development can limit the extent to which recommendations can draw upon economic evidence. Changes in the way WHO Guidelines are developed and interpreted, and how evidence is used to inform decision-making at the country level, is therefore required. We give our thoughts on what these changes could be.

1. Background

The World Health Organization (WHO) produces guidelines for disease management covering a wide range of health conditions (e.g. HIV/AIDS, malaria, child health and nutrition) (WHO, 2014). The guidelines are intended particularly to inform policy and practice in low- and middle-income countries (LMICs) without other established mechanisms to review and synthesize often complex and diffuse sources of evidence (e.g. through use of established health technology assessment processes (HTA)). Guidelines effectively represent “global public goods” that are available for mandated bodies in each country to use and adapt when formulating their own policies. It is intended there are additional processes through which recommendations are tailored to specific contexts. However, the advice of WHO is highly esteemed, and there is typically the perception that close-to-direct adoption of international recommendations is wise or necessary — not least for the receipt of development assistance, upon which the health systems in many countries largely depend (McRobie *et al.*, 2018).

WHO has established processes for the development of its guidelines (WHO, 2014). A Steering Group — convened by WHO and comprised of external experts — provides general oversight, whereas a Guideline Development Group — comprised of experts in the clinical field, programme managers, patient representatives and other stakeholders — produces the core content. An External Review Group, including other relevant stakeholders, reviews the process and recommendations. Content is centered around synthesizing evidence to answer “PICO” questions (in which the population of interest, interventions/comparators and outcomes are all pre-specified) and a recognized approach is followed (known as “GRADE” — Grading of Recommendations Assessment, Development and Evaluation). This leads to recommendations that one or more interventions are deemed effective with a certain level of evidence — i.e. GRADE is used to assess the quality of evidence and recommendations are made by the committees based upon their deliberations (WHO, 2014).

Given the pervasiveness of resource scarcity in all health care systems, but especially in LMICs, where annual per capita national health budgets can be US\$50 or less (WHO, 2018), the extent to which morbidity and

mortality can be reduced by the health care system is primarily limited by resource constraints rather than lack of existence of proven effective drugs and other technologies. Thus, the guideline-setting process is *de facto* often addressing policy issues that are essentially economic in nature — how to spend limited resources amongst a wide range of health care claims that cannot all be feasibly met. However, in almost all cases, they have focused on evidence of clinical effectiveness (although panels are also encouraged to consider intervention feasibility, acceptability, equity and resource use). With a few exceptions, there has generally been very little use of economic criteria used in guideline formulation or even advice on how recommendations could be translated to countries that vary in the availability of resources (Easterbrook, 2014). This raises fundamental questions as to the purposes of guidelines, whether and how economic evidence should be incorporated and how directly or not recommendations can be interpreted for country decision-making on adopting and funding interventions.

In recent years, in one disease area — HIV/AIDS treatment — concerted effort has been made to include evidence from economic evaluation studies into Guideline development. As part of their Consolidated HIV Treatment Guidelines in 2013 (WHO, 2013) and 2015 (WHO, 2016), as well as the 2017 Guidelines on the Public Health Response to Pre-treatment HIV Drug Resistance (WHO, 2017), the HIV Department of the WHO requested the HIV Modelling Consortium (www.hivmodelling.org) to provide consolidated evidence from a number of modelling and health economics research teams. This experience revealed the rigour with which current processes are followed, but also that there are limits in the extent to which policy recommendations draw upon economic evidence, with potentially adverse consequences for the health gains that can be attained from the limited resources available to country health care systems (Hallett *et al.*, 2014).

2. Economic Evaluation in WHO HIV Treatment Guidelines

As part of development of the 2013 HIV Treatment Guidelines, epidemiological modellers and health economists from the HIV Modelling

Consortium were asked to provide cost-effectiveness evidence on two prominent PICO questions:

- (1) When should individuals infected with HIV begin treatment (in the form of antiretroviral therapy (ART))?
- (2) How should individuals receiving ART be monitored for disease progression and treatment switching?

Rather than basing analyses on a single model, evidence was drawn from a diverse set of models to assess consistencies or discrepancies in modelling results.

Overall, there was remarkable consistency in the central findings across models. Clinical evidence from the HTPN 052 trial (Cohen *et al.*, 2011) had suggested that earlier ART initiation reduced the individual risk of morbidity and mortality. Mathematical modelling and cost-effectiveness analyses, which incorporated these mortality and morbidity consequences and the effects of ART in reducing HIV transmission at the population level, concluded that, in countries with high ART coverage, expanding treatment eligibility for HIV positive adults up to the higher threshold being considered (CD4+ cell counts up to 500 cells/ μ l) was likely to be cost-effective (Eaton *et al.*, 2013, 2014). Earlier ART initiation was taken up as a recommendation in the guidelines.

For the second question, modelling showed that more sophisticated forms of patient monitoring (i.e. routine viral load monitoring, instead of more basic clinical or CD4 monitoring) would confer some benefit to patients. However, at the then costs of delivery, viral load monitoring would unlikely represent good use of limited health care resources in most countries. What was deemed clinically effective for patients did therefore not appear to be cost-effective, as assessed when considering other claims upon limited available resources (Keebler *et al.*, 2013, 2014). The panel considered this information, but recommended routine viral load monitoring nonetheless.

For the 2015 HIV Treatment Guidelines, the HIV Modelling Consortium was again asked to design and present analyses that would be useful to the development of the guidelines. The questions were different this time. Instead of modelling being used to provide evidence on the

cost-effectiveness of particular policies that were quite narrowly defined around clinical choices (using PICO questions), the task was to inform how whole treatment programmes could be redesigned in ways to better meet population health needs. For this round of guidelines, the questions were as follows:

- (1) Among whom are HIV-related deaths occurring and what can be done about this?
- (2) How may patient monitoring enable more efficient ART delivery approaches?

For the first question, modelling was used to analyze and extrapolate from HIV population cohort studies in sub-Saharan Africa. It was found that HIV-related deaths mainly occurred among HIV-infected persons not on ART, either because they had not been diagnosed and linked to care or had disengaged from ART programmes (Barnabus *et al.*, 2015). These analyses indicated that greater priority should be given to facilitate diagnosis, entry to care and retention. Moreover, deaths from disengaged patients were expected to increase in coming years, so the modelling highlighted where additional research and new intervention design could be valuable. Modelling was therefore used to take a wider perspective, although it did not, in this instance, formally include an economic assessment.

Following the recommendation for viral load monitoring in 2013 and its subsequent scale-up, the second question aimed at determining how HIV treatment programmes, recognizing their features, could be redesigned to more efficiently meet the challenge of vastly increasing patient numbers. Instead of patients receiving clinical assessments and picking up drugs every one to two months, as was the norm, one option was the introduction of *differentiated care*, whereby stable patients would receive less frequent assessment (e.g. six-monthly or annually) and take home a longer supplies of drugs. Given that viral load testing provides the most definitive indication of which people do not require frequent clinic visits, it was found to be cost-effective if used in this way to support differentiated care. Viral load testing using dried blood spots, which is much easier and cheaper to transport than plasma, was found to be adequate for these purposes (Revill *et al.*, 2015; Philips *et al.*, 2016).

3. Implications and Discussion

Despite the findings of the 2013 and 2015 modelling studies having potentially profound consequences for HIV treatment programmes, they were not necessarily a natural fit within the WHO Clinical Guidelines — structured around PICO questions and based upon assessment of evidence using the GRADE approach.

Economic analysis requires the comparison of the relative merits of alternative policies or interventions that, as a result of resource constraints, cannot all feasibly be delivered. It brings together evidence on clinical effectiveness, costs and opportunity costs into an integrated framework. Since costs and opportunity costs differ by setting, economic analysis is inherently context-specific. When combined with epidemiological modelling, it can address the big questions of programme design in a particular setting, illustrating also the consequences of other supply-side health system features or patient interactions with care that fundamentally affect the health produced from health care provision.

In contrast, the WHO Guidelines begin with clinical questions, framed as PICO questions, for which the GRADE process is used to assess evidence. Within this framework, evidence from randomized control trials specifically is valued most highly. At the culmination of the guideline-setting process, recommendations for policy choice and intervention uptake are made by the guideline development group. The recommendations they can choose are that an intervention is or is not “recommended”, or it is recommended conditional on some other factors. Arguably, this is sometimes done with too little consideration given for context and the knock-on effects of such a change. Although such evidence on clinical effectiveness can be used as an input to economic analysis, it alone is far from sufficient. Whereas WHO Guidelines have been successfully applied to guide choices of what is clinically effective, something that may generalize reasonably well across settings, it is ill suited to inform economic choices.

If WHO Guidelines are to provide useful guidance for countries, then new approaches must be found. If the routine incorporation of economic evidence into guidelines is not feasible any time soon, the limitations of guideline recommendations must be clearly stated — that they are not sufficient to be directly interpreted for policy formulation whenever this

has resource implications. Instead, alternative or additional processes that consider economic criteria are absolutely necessary. This could include the routine incorporation of economic evidence within the WHO decision-making processes, permitting varying recommendations for the very different epidemiological and resource contexts countries face. However, this would require substantial investment to ensure the necessary capacity and data are available. But such capacity is only ever likely to grow if the routes through which analyses can feed into policy deliberations are first made clear (i.e. WHO will need to show how economic evidence can be consistently used in the making of recommendations).

Another approach to setting priorities altogether may, however, in our view, enable even better decision-making. This would be for the WHO and other international organizations to contribute to empowering locally accountable officials to determine policies reflecting the contexts and values held within their own jurisdictions. This can be facilitated by the international community synthesizing and supporting the provision of relevant evidence — clinical, epidemiological and economic. However, ultimately, it will require processes that can better account for the consequence of programmatic factors and resource constraints locally. In an ideal world, and one which we believe the global community should aim to move toward, the analyses themselves would, in the main, also be produced locally. Again, this would require substantial and long-term investment in capacity and data.

A group of stakeholders has deliberated how international organizations, especially WHO in its formulation of guidelines, can better assist countries in resource prioritization (Working Group on Incorporating Economics and Modelling in Global Health Goals and Guidelines, 2019). The Working Group, co-convened by the Centre for Global Development, Thanzi la Onse programme at the University of York and the HIV Modelling Consortium, gave two sets of recommendations. Firstly, to empower countries to develop and analyze appropriate evidence to set health priorities for their populations (e.g. through investment in local analytic capacity). Secondly, to strengthen the WHO guidelines program to inform resource allocation (e.g. by establishing clear and robust principles, methods and standards for economic evidence to be included within WHO guidelines). The current WHO Guideline development processes are

insufficient for formulating policies with resource implications, and other approaches specifically oriented toward this objective must be developed.

Key Messages

- Country-level decisions about health policy and implementation are typically as much economic in nature (i.e. concerning the allocation of scarce health care resources) as they are about choosing interventions on the basis of clinical effectiveness alone. In many LMICs, there is some reliance upon international organizations for both funding and guidance.
- WHO Guidelines hold particular influence by informing countries on disease management for a wide range of conditions. Established processes are followed to assess evidence on which interventions are likely to be *effective*; but if policies are then formed without due consideration of the consequences of *resource use*, there can be adverse outcomes due to inadvertent drawing of resources away from other more impactful health care investments.
- HIV/AIDS treatment is an area in which efforts have been made to incorporate evidence from the modelling and economic evaluation studies into WHO Guidelines. This highlighted, amongst other things, that what is *effective* is not always *cost-effective*, and that some of the greatest causes of HIV-related mortality and morbidity might be better addressed through supporting appropriate patient engagement in care, rather than a more limited focus on choices of clinical interventions alone.
- Although the value of contributions from modelling and economic evaluation to inform global health priorities is recognized, the current approaches followed in the development of WHO Guidelines are not oriented to the formal consideration of economic criteria. Steps are now being taken by WHO and its partners so that, in future, guideline recommendations may hopefully better contribute to policy decisions on resource allocation taken at the level of countries.

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