ANTIBIOTIC INNOVATION– SOME LESSONS FROM THE WHO PROCESSES ON PUBLIC HEALTH, INNOVATION AND INTELLECTUAL PROPERTY

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In this article we discuss the relevance for development of new antibiotics from the main conclusions of the report of the Consultative Expert Working Group on Research and Development (CEWG). This report is part of a work stream that was initiated by the WHO in 2003, leading to the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property Rights in 2009. Subsequently, the CEWG Report was published in 2012. It assessed a number of proposals that aim to strengthen global financing and coordination of R&D for diseases disproportionately affecting developing countries, the so-called neglected diseases.

Specifically, we ask: how can intellectual property rights (IPR) be mobilized and harnessed in ways that contribute to a feasible economic reward model for sustainable access to effective antibiotics, and in this respect what experiences can be drawn from the field of neglected diseases generally and from the recommendations proposed by the CEWG in particular? We conclude that innovative IPR licensing practices and open source R&D collaboration models can be used as buildings block, together with interventions such as pooled funds, direct grants, prizes, and access maximizing pricing, in designing a comprehensive framework for new antibiotics that strengthens innovation, secures universal access and promotes rational use.

Practitioners, policy-makers and researchers within the field of global health may have grown accustomed to the sad fact that, frequently, drugs that are directly needed by vulnerable patients are not being developed due to lack of profitability or to markets with low purchasing power. With emerging antibiotic resistance and the concurrent lean antibiotics R&D pipelines the striking feature is likely not the novelty of that challenge, but the fact that in this specific case the potential victims to the public health threat are not only poor people in faraway countries, but also patients and consumers in high-income countries.

On the other hand, a different problem in the antibiotics field is that excess use compounds the all too familiar problem of lack of access. Irrational use of antibiotics leads to quicker evolution of resistance in pathogenic (and non-pathogenic, so called normal flora) bacteria than would otherwise be the case.

The all too small trickle of candidate antibiotic drugs in the pipelines calls for new economic reward models to incentivize innovation. However, such reward models should not only ensure a sufficient return on investment to the drug developer since somebody has to cover the costs. They should also, in an integrated and coherent way, ensure equitable access to new antibiotics on a global scale to those that truly need them, as well as ensure their rational use. Together these measures could secure sustainable access to effective antibiotics in the years to come.

Despite persistent unmet needs for drugs, vaccines,

diagnostics and other essential health commodities and technologies in low- and middle-income countries, there have been encouraging interventions and initiatives to strengthen and promote R&D efforts targeting neglected diseases. We believe some of the experiences in the field of neglected diseases are very relevant to discussions about how to resolve the currently unfolding antibiotics crisis. Nevertheless, in the following we will explain that there are important differences between neglected diseases and infections caused by emerging resistant bacteria, which impedes direct transfer of experience, solutions and economic models from the one to the other.

Thus, the main question to be discussed in this article is: how can IPR be mobilized and harnessed in ways that contribute to a feasible economic reward model for sustainable access to effective and appropriate antibiotics, and in this respect what experiences can be drawn from the field of neglected diseases generally and from the recommendations proposed by the Consultative Expert Working Group on Research and Development (CEWG) under the auspices of WHO.

First, we will discuss similarities and differences between diseases caused by resistant bacteria and neglected diseases in order to provide a general idea of the extent to which experiences with different interventions in neglected diseases are transferrable to the antibiotics field. We then give a brief account of the process leading up to the publication of the CEWG report. Lastly, we discuss six selected proposals that were recommended in the report in light of their relevance for antibiotics innovation and stewardship, while simultaneously introducing a few other relevant ideas.

Diseases caused by resistant bacteria are Type I diseases

In global health discourse diseases for which appropriate treatment is lacking are termed "neglected diseases". We use the following classification to illustrate some schematic points.

Type III diseases are those that are overwhelmingly or exclusively incident in developing countries, such as bilharzia (schistosomiasis) and ebola *(1)* (p 18). For many Type III diseases the main problem is that appropriate treatments simply do not exist, basically because of lack of purchasing power on part of the potential patients, or the governments in their countries of residence, means that incentives for R&D are weak.

Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries, such as hepatitis, tuberculosis and HIV. For many Type II diseases treatments exist, but in many cases drug patenting facilitates monopoly prices which means that patented medicines are out of reach for poorer populations.

Type I includes diseases that are incident in both rich and poor countries, with large numbers of vulnerable populations in each, and thereby not "neglected" as such. In this typology most antibiotic resistant infections fall within the Type I category, being as it is a truly global challenge. For instance, the UN Commission on Life Saving Commodities for Women and Children listed injectable antibiotics to treat sepsis in newborns as one of the 13 most important commodities addressing leading avoidable causes of death during pregnancy, childbirth and childhood *(2)*.

Apart from the geographical distribution the other important difference between antibiotic resistant infections (Type I) and Type III diseases is the nature of the market failure. While in Type III developing and manufacturing appropriate medicines are not profitable, with antibiotics there should realistically be sufficient purchasing power in high-income countries to achieve a positive bottom line. The problem is rather that the opportunity costs to the innovating companies are too high given other more profitable disease areas *(3)*.

A common problem in infectious diseases of all three types is of course the emergence of antimicrobial resistance. In antibiotics resistance develops as a function of the distributed volumes, thereby limiting their profitability. Moreover, given that users/agencies will seek to ration an antibiotic drug in order to avoid development of resistance and hence preserve its effectiveness, there is also an element of financial risk and unpredictability in antibiotics R&D investment decisions.

It is important to note, however, that high-income countries are better equipped for combatting and controlling infectious diseases than low-income countries in terms of sanitation, public health measures, immunization programmes and health-care systems. In this way also Type I infectious diseases impact more strongly on poor people in low-income countries than on people in high-income countries.

To sum up, interventions on the antibiotics field should incentivize innovation and ensure global access, much like what CEWG set out to achieve in Type II and III diseases. In addition, appropriate interventions should prevent excessive use.

The CEWG Report

The Consultative Expert Working Group on Research and

Table 1: **The 15 groups of proposals for stimulating R&D assessed by the CEWG. Adapted from *(1)*. The six groups that best met the evaluation criteria are in bold italics**

Proposals assessed by the CEWG	
Global framework on research and development	***Open approaches to research and development and innovation***
Removal of data exclusivity	***Milestone prizes and end prizes***
Direct grants to companies	Purchase or procurement agreements
Green intellectual property	Priority review voucher
Health Impact Fund	Regulatory harmonization
Orphan drug legislation	Tax breaks for companies
Patent pools	Transferable intellectual property rights
Pooled funds	

Development (CEWG) Report represents the end result of a cascade of resolutions and reports that was initiated at the 56th World Health Assembly (WHA) in 2003, where the World Health Organization (WHO) Secretariat presented a report on intellectual property, innovation and public health, whose main focus was on the need for looking at mechanisms for stimulating innovation and at the relationship between intellectual property rights and public health *(4)*. Nine years later, following two resolutions and a report by an international commission *(5)* and a negotiated global strategy and action plan *(6)* and one working group *(7)*, in 2012 the CEWG Report was published under the auspices of WHO[1]. The report assesses a range of different proposals for strengthening financing and coordination of R&D for neglected diseases.

The main task of the CEWG was to "to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of financing to stimulate research and development" for neglected diseases, by building on the above mentioned previous processes and reports. More than 100 proposals from the previous reports and proposals solicited from different stakeholders that were considered to be within the mandate of the group were reviewed and grouped into 15 main categories (see Table 1), of which six were considered to best meet the evaluation criteria. In the following, we will discuss all of the six while adding some ideas that were not included in the CEWG assessment.

Delinking and decoupling

In order to finance R&D related to Type III diseases the CEWG report argues for delinking revenues and R&D costs, while in antibiotics we also wish to decouple revenues and volumes. What does this mean?

The basic pharmaceutical company business model consists in covering initial R&D costs by generating downstream revenues based on high prices facilitated by monopoly market power through patents. Delinking R&D costs from revenues and price means to cover the R&D costs by other means, for instance by public sector interventions. For Type III diseases Product Development Partnerships are but one delinking mechanism.

Similarly, the business model entails having manufacturing costs covered by maintaining a revenue stream based on high volumes. In antibiotics, however, even if R&D costs are delinked, drug stewardship (and indeed, resistance development) might limit sales to the extent that not even manufacturing costs are covered since many new antibiotics will be shelved for third or fourth line treatment. In addition, there is agreement for the need to avoid financial incentives for oversale, overuse or overprescription. Hence the need for also decoupling revenues from volumes, i.e. somehow the manufacturing costs must be covered independently of the sold quantities.

Cut short, the need for stewardship in antibiotics adds decoupling to the delinking requirement. The CEWG report did not see delinking as a proposal per se; instead it was used as one out of nine criteria for evaluating the different proposals[2].

Open approaches to research and development and innovation

The CEWG report gives an overall positive, but yet conditional, assessment of the Open approaches, which includes the following five interventions and measures.

Open innovation is an R&D strategy that aims at sourcing knowledge and information across organizational boundaries, commonly by establishing research networks and other means of collaborative operational procedures. Precompetitive R&D platforms are a subset of open

[1] One of the present authors (JAR) chaired the CEWG.

[2] The other criteria were: public health impact, efficiency/cost effectiveness, technical feasibility, financial feasibility, intellectual property, access, governance and accountability, and capacity building.

innovation, and refer to collaborative efforts at developing technologies that are not intended to be patented as such, but which aim to overcome problems in the overall research process in any given field. One example is the DRIVE-AB project, which aims at developing an economic reward model for antibiotics innovation and stewardship[3].

In our view, these two ways of organizing R&D have great potential for stimulating antibiotics R&D. We believe public funds should be used to finance innovation models that source R&D efforts from a multitude of commercial and non-commercial entities, much like the operational procedures for many of the Product Development Partnerships (PDPs). Indeed, our impression is that several PDPs actually practise open innovation, albeit without necessarily self-declaring to do so.

In its strictest sense, open source in its original version from the computer software industry does not translate directly into drug development, primarily because of the differences in managing copyrighted software source code on the one hand and patented molecules on the other. However, in the adapted version introduced by the CEWG open source drug discovery entails an open approach to IP, that is, making data and papers publicly available, and allowing IP rights to be used freely by collaborators (and others) by customized licenses or the use of public domain.

The CEWG viewed the potential of the Open approaches to lie in reduced R&D costs, possibilities for delinking, and more collaboration and broad participation in R&D processes. They are technically feasible, and seem to be particularly applicable in earlier stages of the development process. The qualification is that these Open approaches have been implemented and tested to a limited degree only, so that evidence on their feasibility and efficiency is still somewhat scant. In sum, despite addressing access issues mostly in indirect ways, Open approaches were considered to meet many of the assessment criteria in contributing to R&D.

We believe that up to the clinical trial level an antibiotic drug development process can be facilitated by open source measures in combination with other interventions *(8)*.

However, in antibiotics specifically one aspect of the IP issue is turned inside out, as it were. In Type II diseases transfer of IP rights to generic manufacturers commonly appears as a measure to introduce competition and hence price reductions, which in turn contributes to universal access *(9)*. However, in antibiotics unrestricted generic manufacturing and sales may hold the potential to undermine rational use. Or, controlling IP rights to new antibiotics can be a key instrument for effective stewardship, at least in the short to medium term, i.e. the duration of the patent protection. Such IP rights could be acquired by an international public entity for instance by way of a patent buy-out, and sub-licencees would be obliged to comply with defined conservation or stewardship measures. Thus, in the absence of a strong and well-functioning global framework or regulation for antibiotic stewardship, universal access may need to be ensured by other means than free generic manufacturing and sales. We wish to underscore, however, that using IP rights as a stewardship instrument immediately raises many concerns including the highly critical issue of who is supposed to control those rights. Most likely, a publicly controlled entity would be most appropriate. We also wish to reiterate that global stewardship by IP control must be implemented with participation by an international range of stakeholders, including representatives from different countries; that imposes stewardship regimes that are appropriate for the different national and regional contexts; and that are linked to other interventions to improve access and rational use.

These lines of thinking link directly to the last proposal that the CEWG considered under the Open approaches headline, namely equitable licensing, which is a set of defined strategies for managing IP rights. This set of principles for IP licensing for global access aims at increasing access to pharmaceuticals by facilitating generic manufacturing, technology transfer and further research. Within this framework[4] "at-cost" provisioning is considered a second best alternative to generic provisioning. Translated into a hypothetical situation in which IP is being used as a stewardship instrument, conditional non-exclusive licensing appears to be a strategy for achieving the dual goals of access without excess. The non-exclusivity would facilitate universal access, while the conditions would seek to avoid excess. In short, this would be a model for restricted and supervised generic manufacturing.

An access interlude – tiered pricing

In the absence of (restricted) generic manufacturing there is one alternative measure available for promoting universal access that the CEWG considered to be outside of its mandate since it does not directly incentivize innovation. On the global vaccine markets suppliers have offered vaccines at tiered prices, or differential prices. In parallel, consumers have established pooled procurement mechanisms, most

[3] The DRIVE-AB projects involves more than 20 organizations, including industry partners. The present authors are active partners. See http://drive-ab.eu/

[4] http://uaem.org/cms/assets/uploads/2013/03/GlobalAccessLicensingFrameworkv2.pdf

notably those operated by the UNICEF Supply Division (SD) and the Pan American Health Organization's Revolving Fund (PAHO RF), and this combination of market behaviour by monopolies on the supply side and monopsonies on the demand side has resulted in prices for many off-patent vaccines approaching marginal manufacturing cost in developing country markets *(10)*. It is important to note, however, that in principle tiered prices is a profit maximizing measure employed by the supplier which, in the absence of counteracting measures on part of the consumers such as for instance pooled procurement, will entail perfect price discrimination, and the opportunity for selling at monopoly prices in both high-income and low-income markets, albeit at a lower price in the latter. This means that low-income country purchasers get a lower price than what would be the case if the product was sold at a uniform price, but the low-income country price is still higher than what would have been the case in the presence of generic competition, for instance.

Thus, although tiered pricing of new antibiotics might generate a certain revenue stream in high-income markets while to some degree increasing access in low-income markets, universal access requires additional measures on part of consumers or third parties.

The conditional non-exclusivity licensing model above could be complemented with the IP holding entity marketing antibiotics at different prices in different markets, but by setting prices that maximize access in line with responsible use instead of maximizing profits, i.e. implementing principles for access maximizing pricing. We decidedly do not recommend using prices at the point of care to limit the use of a new antibiotic, since uneven purchasing powers of the different users would make this an overly blunt, imprecise and inequitable instrument.

Compounding the access issue is the fact that most likely new second and third line antibiotics will not be oral but injectable. In particular, in low-income settings intravenous drugs can be a challenge, as can the stability of the formulation. Thus, universal access to these antibiotics will not only depend on affording the drug itself, but might also require universal access to functional health facilities and hospitals as well as trained providers; a far cry from current realities in many low- and middle-income countries *(11)*. We also see universal access to point of care diagnostics as indispensable tools for rational use.

Patent pools

Typically, patent pools are formed by patent holders whenever the technology in question is subject to patenting by several patent holders in a way that makes it difficult for each of them to determine how to implement the technology in manufacturing without infringing, or appearing to infringe, on the other patents holders' claims. Such a situation is quite common in the electronics and telecommunication industries with complex products.

The CEWG gave a high rating to the three patent pools that were assessed, of which one will be mentioned here[5]. Specifically, CEWG assessed the Medicines Patent Pool (MPP), funded by UNITAID,[6] as one of the model examples in this category. MPP deals with patents related to products for treatment of HIV/AIDS. This therapeutic area is dominated by combination therapies, that is, most drugs used in the treatment regimens consist of several patented chemical components, and commonly these patents are distributed among several different companies and entities. Thus, for an entity developing combination HIV/AIDS drugs negotiating licenses with all the relevant patent holders can involve both high administrative costs and a high degree of uncertainty and risk.

Taking the CEWG assessment as a point of departure, to what extent are patent pools relevant and feasible in designing economic reward models for incentivizing antibiotics innovation, and in securing access and rational use? In antibiotics, the above mentioned risk and cost reducing properties of a patent pool seem to be evoked first and foremost whenever the drug in question consists of several patented molecules or compounds owned by different entities, or if for some reason licensing of several process patents should be required to set up the manufacturing process of a single molecule drug or otherwise combine technologies, or if there are patented technologies that are necessary further upstream in the innovation process. Nevertheless, given that cross-resistance might occur between different antibiotic drugs within a class, it could be appropriate to jointly manage the IP rights within each class by way of a patent pool. And to our knowledge there is nothing to prevent the MPP from also managing IP rights for antibiotics.

Next, we will be looking at the three CEWG proposals that are relevant for the delinking/decoupling argument mentioned above, namely direct grants to companies, milestone prizes and end prizes, and pooled funds.

Direct grants to companies

The basic idea under this heading is to provide public funding to small and medium sized enterprises in "innovative"

[5] The other two were the Pool or Open Innovation, established by GlaxoSmithKline, and the Re:Search, launched by WIPO.

[6] For more information about UNITAID please see http://www.unitaid.eu/

developing countries, much like the United States Small Business Innovation Research Initiative (SBIR)[7] operated by the National Institutes of Health. Even though such funding is likely to be aimed at the early stages of drug development processes, the CEWG report cited evidence from the United States suggesting that there can be significant public health impact of such interventions.

We believe that biotech and "one-product" start-up companies worldwide having antibiotics and bacterial diagnostics in their pipeline can be effectively supported by such schemes. Indeed, the New Drugs for Bad Bugs programme (ND4BB) under the Innovative Medicines Initiative (IMI)[8] and the Biomedical Advanced Research and Development Authority (BARDA)[9] grants of the US Department of Health and Human Services fall within this category. Grants can be awarded on conditions related to rational and equitable marketing of the final product, and to licensing strategy. In this sense, direct grants can contribute to both delinking and decoupling. However, to our knowledge, neither IMI nor BARDA have incorporated conditions like this in their funding models.

Milestone prizes and end prizes

Such prizes are rewards for successful completion of a specified set of R&D objectives. They can be linked to specific milestones in the R&D process, or to a Target Product Profile of a desired end product. The CEWG report points out the advantage of paying for success only, and of having the option of imposing specific licensing conditions on the award winner, including a patent buy-out as suggested above. As such, they have considerable potential for delinkage, but they require careful set up of governance institutions and clear rules and eligibility criteria to work properly. Moreover, conditions related to IP could contribute to decoupling.

In antibiotics, prizes for point-of-care diagnostics were recommended in a recent Report to the President of the United States by the Council of Advisors on Science and Technology *(12)*, and indeed, the Longitude Prize 2014, which opened in November 2014, awards £10 million to inventors of a cost-effective, accurate, rapid and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotics at the right time[10].

In our view, the flip side of the advantage of the no-cure-no-pay principle is that much of the risk needs to be carried by the product developing entity alone, which means that cash-constrained companies might not be incentivized. This is not in line with many actors arguing for risk sharing models in antibiotics development *(13)*. This is less of a disadvantage with milestone prizes than with end prizes, however. Bearing the above CEWG caveats in mind, we believe prizes, much like any other intervention discussed here, may work well in concert with other reward mechanisms.

Pooled funds

This group of proposals in the CEWG report is based on the common idea of having one entity managing funds from multiple stakeholders and donors by allocating grants to designated R&D purposes, be it Product Development Partnerships, small and medium sized enterprises (in developed and developing countries), pharmaceutical companies, research institutions, or any other kind of relevant entity. Although these intervention ideas need some further elaboration and development, their potential strength would have to be proven in terms of their ability to generate additional funding in innovative and sustainable ways.

Given the global scope of the antibiotics crisis, the relevance of pooled funds is quite obvious. From a more microeconomic perspective pooling is also a requirement for decoupling and delinking since moving away from only relying on unit based revenue streams means that purchasing power needs to be pooled at one level to aggregate demand, at least at the health system or health insurer level. This pooling will also be able to facilitate pooling at the national or supranational levels. Pooled funding could both delink revenues from R&D costs and decouple revenues from volumes. Decoupling would take place for instance by using pooled funds to pay a manufacturer for the production costs independently of the volumes actually purchased through e.g. a service level agreement where the manufacturer guarantees provision of a volume within a boundary. Such a set-up would fit well with the sixth and last CEWG proposal to be dealt with in this article.

Global Framework on Research and Development

The CEWG considered a Global R&D Framework to be ambitious, but also to have the virtues of transparency, participation, effectiveness in governance, global coordination of R&D, and generation and allocation of funds.

[7] http://sbir.nih.gov/

[8] The above mentioned DRIVE-AB project (p) is funded by IMI. See http://www.imi.europa.eu/.

[9] See http://www.phe.gov/about/barda/Pages/default.aspx

[10] See http://www.longitudeprize.org/. One of the present authors (JAR) is in the advisory group of the Longitude Prize 2014.

In our view, a global framework in antibiotics would have the primary purpose of ensuring responsible use. Funding for antibiotics R&D will most likely be provided by high income countries, so we see a true Global Framework first and foremost providing the resources necessary for securing decoupling. In this way, a Global Framework could have provisions for how to market, dispense, distribute and prescribe antibiotics in ways that both limit resistance development and increase access. Such a framework could be part of a more comprehensive package of measures.

A Global Framework can then be supported by a more limited multi-country-based agreement where a coalition of committed states could pool their resources to contribute to pooled funds for antibiotic development and require this to happen under the globally agreed framework that first and foremost handles responsible use.

Conclusion

The performance of the traditional reward model of selling patented drugs at monopoly prices is not satisfactory in terms of providing needed drugs against neglected diseases and antibiotics against common bacterial infections. The traditional model is both failing to bring new antibiotics to the marketplace at a satisfactory rate and to ensure a sufficiently rational use of existing and future antibiotics.

There are interesting and relevant lessons to be drawn from the field of neglected diseases in global health discourse, both in the form of practical experiences such as PDPs and in the form of reports and analytical efforts and policy discussions such as the CEWG and its follow up. However, there are important differences between "traditional", mostly tropical, Type II and III neglected diseases on the one hand and antibiotic resistant infections of Type I on the other which call for caution in translating those lessons from the former field to the latter.

For instance, although generic manufacturing can facilitate access, it may also facilitate excess, since it does not ensure rational use. Contrary to the case of Type II and III diseases, controlling IP rights can be important in implementing a non-paternalistic, participatory, transparent and context sensitive regime for rational use of new antibiotics. Along this line of thinking a public patent owning agency and any licensees can market patented antibiotics on conditions that would secure rational use, for instance by requiring prescriptions or similar arrangements based on defined diagnostic criteria only. IP protection may not be the only way, though, as sustainable solutions also need to address the post patent expiry period.

Indeed, we do not assume that any of the following proposed interventions can possibly solve the antibiotics crisis in a satisfactory way in isolation. The point to be made here is rather that innovative IP licensing practices, patent pools and open source R&D collaboration models can be used as building blocks, in combination with measures such pooled funds, direct grants, prizes, and access maximizing pricing, in designing a comprehensive global framework for new antibiotics that strengthens innovation, secures access and promotes rational use. One of the great challenges ahead is to develop models for operationalizing and implementing a comprehensive and coherent set of appropriate measures.

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