CREATING AN INTERGOVERNMENTAL CONSORTIUM FOR NEW ANTIBIOTICS: A NEW DEVELOPMENT MODEL

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All countries in the world are facing increasing levels of resistance to existing antibiotic treatments. In recent decades, only two new classes of antibiotics have come to market, although around 60 derivatives of existing classes are in the pipeline, of which few are targeting Gram-negative bacteria. The creation of a new system of rewards for innovation and development of new antibacterial drugs has come to the fore as a matter of urgency.

The world needs to develop the means to bring about new antibacterial products, while working in parallel on strong regulations on the availability and use of the new drugs in human and/or veterinary medicine, in order to prevent the occurrence of resistance.

We present here the concept of an "intergovernmental consortium for new antibiotics", a new development model to promote and finance R&D and production of medicines against bacterial infections. Such a new model could have the following features:

1) mostly public sector funded research and clinical trials;
2) grants to small and medium-size innovative companies or universities to develop new products;
3) milestone and end prizes to reward innovation;
4) patent pools to bring together intellectual property rights generated by public sector-funded research;
5) production and marketing agreements for a needs-based number of treatments per year;
6) an intergovernmental consortium to manage the distribution and preservation of new antibiotics.

The above 1), 2) and 3) elements have potential for decoupling rewards for research from product sales revenues.

Introduction: Public health needs in the "post-antibiotic" era

"The world is moving towards a post-antibiotic era in which common infections will once again kill" declared World Health Organization's Director-General, Dr Margaret Chan *(1)*.

Antibiotic resistant bacterial infections affect 5 million patients hospitalized every year in the wealthiest parts of the world – United States and European Union, and kill 50,000 patients, figures rising, the situation is indeed serious *(1)*. Advanced medical practices such as transplantations and cancer treatments are impossible without working antibiotics. Years of medical practices could be put in jeopardy, and tomorrow a minor bicycle injury could mean death, as was the case a century ago. Conclusive research shows that countries with lesser levels of economic development face the same problem.

In general, bacterial diseases still contribute heavily to the global burden of disease; they are a major factor in mother-child morbidity and mortality, strike heavily at young children and young adults. Drug resistance has been inexorably climbing in low- and middle-income countries (LMICs), as has been now documented for more than a decade *(2)*. Neonatal sepsis, pneumonia, tuberculosis and meningitis are examples among many where bacterial resistance has been identified. Pneumonia is the most common cause for adults being hospitalized in sub-Saharan Africa – 4 million episodes – and accounts for 200,000 deaths a year *(3)*. A hospital study in Tanzania showed that

Gram-negative sepsis in children had a mortality rate twice that of malarial infection *(4)*. Nearly a quarter of *Streptococcus pneumoniae* strains are reportedly resistant to three classes of antibiotics *(5)*.

Across Africa and Asia, the resistance of bacillary dysentery in children to ciprofloxacin – the treatment recommended by WHO – has risen from negligible to 30% in a decade *(6)*. Drug resistance to gonorrhea has arisen in waves, first to fluoroquinolones, then to cefixime, and more recently to azithromycin *(7)*. While a protective vaccine exists for some of these conditions, many must rely on antibiotic treatment *(8)*.

Low-income populations, which have access to antibiotics mainly through cheaper generics will be at risk from the rise of bacterial infections resistant to first- and second-line treatments as third-line treatments of which no generic versions is available due to patent protection will often be unaffordable.

Antibiotic resistant pathogens recognize no political borders or frontiers and represent a very important global risk. It has been identified as such by the WHO *(9)*, the G8 *(10)*, the World Economic Forum *(11)*, and many governments of countries from all income levels, from the United States administration to the United Kingdom authorities, and from China to India or South Africa, as well as by large constituted networks of scientific societies and committed individuals *(12, 13)*. Indeed, the rise and spread of a bacterial gene which confers resistance to a broad range of antibiotics, first discovered in United Kingdom patients returning from India, identified in the wastewater of New Delhi, and named "NDM-1" (New Delhi Metallo-beta-lactamase-1), has now been identified with alarm all around the world: in China, Pakistan, the United States and European countries. NDM-1 has been identified in 18 countries from all continents over the span of one year. As the gene travels via human gut microbiota, the epidemiological consequences are awesome: global outbreaks of totally antibiotic resistant diarrheal and other diseases are looming *(14)*.

The need for a new innovation model

The objective of this proposal is to suggest a new model for research, development and distribution of new classes of antibiotics.

Everywhere national plans for rational use of antibiotics and to mobilize societies against resistance are coming into being. Antimicrobial resistance is now a key topic at the World Health Assembly, and has been the topic of many inter-ministerial meetings *(15)* as well as national emergency announcements since June 2014 *(16)* .

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In the array of antimicrobials antibiotics occupy a unique place from the standpoint of research and development needs and implications.

We do not get the antibiotics we need

It has now been publically acknowledged by all public and private stakeholders that the R&D pipeline for novel classes of antibiotics has faltered *(17, 18, 19)*.

There are several explanations for this state of affairs:

- Low hanging fruits have already been collected: easily developed molecules with antibacterial properties have already been investigated, generally from stored compounds by the large pharmaceutical companies. "New" antibiotics are more difficult to identify and develop, and hence more costly to bring to market.
- Public pharmaceutical research is often strapped for funding in many countries, while small and medium size innovators may lack access to sufficient funding.
- Market prospects are better in other areas. Antibiotics are short course treatments and do not compare well as an R&D investment with drugs for lifelong ailments such as hypercholesterolemia, diabetes or other noncommunicable diseases.
- The need to maintain the effectiveness of any really new antibiotic by restricting its use to patients with ailments not responding to treatments, diminishes the financial rewards that any private entity would expect from investing in R&D. In fact new antibacterial entities may be considered rare and precious resources.
- Mechanisms should and will be put in place to prevent widespread use of antibiotics in human health.
- Clinical development today would need to be conducted on patients with antibiotic resistant infections and the

lives of a hypothetical placebo group would be at risk, raising difficult ethical questions.

- Newer products may not be allowed for use in animal health (which represents over 50% of global sales today).

As in the case of diseases of poverty or neglected diseases, the market alone does not assure sufficient investment in research and is not needs driven, thus not necessarily focusing on the products that are most needed.

The bottlenecks are not just financial, but also of a scientific and regulatory nature. The drive to discover new drugs should be accompanied with a commitment by all countries to make sure the new antibiotics will be used sparingly so they will remain effective for some years since any large scale indiscriminate use would, in fact, spur natural bacterial resistant mechanisms overnight.

The commitments of countries should also include access for all patients in need, independent of financial status, anywhere in the world.

Therefore we are facing the need to reconcile developer incentives with the preservation of the resource.

New and innovative approaches and mechanisms to support the financing and coordination of R&D

There are several viable ways to foster R&D for innovation. Of particular interest are the mechanisms 1–3 described below, as they are potentially a means of delinking R&D from marketing a product, which would be crucial to resolving the antibiotic challenge in the interest of all. In a Chatham House seminar paper, law professor Kevin Outterson wrote : "Antibiotic delinkage may offer the most promising avenue for a sustainable, global approach. Delinkage recognizes that rewarding producers and sellers on the basis of volume is fundamentally inappropriate" *(20)*. Outterson lists all the diverse schemes proposed recently and states that a significant number of CEOs from the pharmaceutical industry have come to endorse the idea. Among the WHO demonstration projects presented early 2014, an Antibiotic Innovative Funding Mechanism (AIFM) was selected by the European Union region *(21)*.

1. Public-sector funded research and clinical trials

The history of medical research shows that public sector-funded research has consistently played a key role in discovery of medical products. For the research of new antibiotics, the knowledge of traditional healers would need to be tapped for potential new classes of compounds, and attention should be brought to natural substances. Indeed, between 1982 and 2002, 70 of the 90 antibiotics reaching market came from natural product sources *(22)* . In this regard, it should be noted the biodiversity needed to search for potentially effective natural substances is often richer in low-income countries.

Historically, a European example of publicly-funded inter-country collaboration is CERN, the European Centre for Nuclear Research, which continues to bring together scientists from all of Europe, even at the height of the Cold War, to study the origin of our universe. CERN was the cradle of the World Wide Web, the "www", which we all use daily today. A March 2014 Geneva Graduate Institute event on antimicrobial resistance concluded that such a publically funded "CERN-like" research centre could be envisaged as a way to strengthen research and innovation for new antibiotics, although a major difference is that antibiotic research does not require the same huge infrastructure as the research carried out in CERN. Another interesting model of an international publicly-funded research institution is the International Agency for Research on Cancer (IARC). IARC is a specialized agency of WHO, established by a resolution, but independently governed and supported by regular budget contributions paid by participating countries and extra-budgetary resources secured through competitive grants from funding agencies.

Clinical trials will be required to assess safety and efficacy. This is considered the most "costly" part of the pipeline approach to drug production by industry. Therefore public funding for clinical trials would be important to speed up the trials, make sure they are ethically correct, that they are transparent, and open to scrutiny so as to avoid drugs with little innovation.

2. Grants to small and medium size innovative companies or universities

Grants are a common mechanism through which funding is allocated for research projects. In the case of antimicrobials, grants could be set up by public entities for small or large companies to assist in perfecting and optimizing the new antibiotics.

3. A Prize system

Prizes can be of two sorts: End Prizes and Milestone-intermediate Prizes. WIPO recently included a discussion on innovation inducement prizes and delinking at its Committee on Development and Intellectual Property (CDIP) Fourteenth Session *(23)*. Some high-income countries are envisioning this option on a national basis. In the United States, the President's Council of Advisors on Science and Technology, (PCAST) September 2014, latest document on antibiotic resistance has

a whole chapter on de-linking and envisions a large "financial reward", a Prize: "Under such schemes, a successful developer of an antibiotic that addresses an important public health need would receive a financial reward that is not directly tied to the usage of the drug" *(24)*. In the Chatham House seminar paper, Professor Outterson lists all the diverse "prize" schemes. Among the WHO demonstration projects presented early in 2014, was the Antibiotic Innovative Funding Mechanism (AIFM) prize.

In the history of scientific discoveries, a close look demonstrates that cooperation and serendipity nourish scientific discovery. Major outcomes came from public endeavours when scientists were left to search for solutions, without administrative restrictions. It is also the case that major breakthroughs did not emerge from spontaneous generation in one genial brain, but rather grew from the fertile seeding of innovations, "incremental milestones" findings of many innovators which provided the terrain in which the "genial" mind could make the breakthrough. Hence, perhaps, most important to consider are "milestone" or interim, incremental result prizes in the quest to find innovative antibiotics.

This feature is important for many small biotech enterprises or research departments in universities who, by themselves, may not have the capacities to bring a product to fruition but which are frequently imaginative breeding nests for innovations.

Milestone Prizes entail recognition of very early discovery – before the definitive proof of principle of the innovation. These intermediate prizes should be sized so that they would be attractive to academia from applied or fundamental research fields. It would also attract small and medium size enterprises (SMEs), including from LMICs. It should be expected that entities entering the Milestone Prize contests would accept – in case they win a reward – to give a right of first refusal on their intellectual property rights to the publically managed intergovernmental consortium.

The UK Longitude Prize of £10 million, which was voted by the public in 2014 to go towards diagnostics to help identify antibiotic resistant infections and to assist in the rational use of antibiotics, is a good example of an "End Prize" *(25)*. The United States' President's Council of Advisors on Science and Technology PCAST envisions very high level End Prizes to be offered by the United States government for the discovery of novel antibiotics *(26)*.

End Prizes should entail a very high financial reward for a fully developed antibacterial drug. It should be expected that entities entering the End Prize contests would accept – in case they win the reward – to assign intellectual property right to the publicly managed intergovernmental consortium.

4. Pooling patents to bring together intellectual property rights generated by public sector funded research

In effect, all the rights to inventions which successfully obtained a Milestone Prize and the outcome product of the End Prize would end up into a publically managed patent pool that would be set up by the consortium. Historically patent pools have been in existence for quite a while. The best known is FD Roosevelt forcing two competing plane manufacturers to merge their intellectual property *(27)*, so that the United States could build an air force capability to enter World War II.

The Medicine Patent Pool (MPP) Foundation that was set up with the support by UNITAID, is a prime example of what a patent pool is all about and how it works. Using patent pools to facilitate access to medicines was an idea spearheaded by a number of nongovernmental organizations (NGOs), including Knowledge Ecology International (KEI) and the international NGO Médecins sans Frontières (MSF) who initiated a campaign for a patent pool back in 2006, and applauded when the MPP was launched in 2009, while continuing to demand that access for all had to be the driving motive. The MPP advocacy description stipulates that patent pools allow for easy access to latest medicines for LMIC poor populations; facilitating low-cost manufacturers production of new medicines easily and rapidly; and the pooling of innovations to develop combination therapies. The MPP was considered a model pool by the WHO "Consultative expert working group on research and development: financing and coordination." (CEWG), in its April 2012 report.

Another example of pooling scientific knowledge and making available research results is the new Re:Search of the World Intellectual Property Organization (WIPO) *(28)*.

The consortium would manage the pooled intellectual property and provide licenses to countries that allow for the manufacturing of the new antibiotics. Conditions for obtaining a license would be such as authorized production would not result in indiscriminate large scale distribution of the new antibiotics, in order to prevent rapid onset of resistance. Indeed, self-regulation by users and prescribers would not result in elimination of overuse and misuse of new antibiotics, judging from past and present experience. Such license conditions could be for example restriction of use for human medicine, limited production, sales to authorized entities (such as hospitals) only.

5. Production and marketing agreements

Purchase agreements with private industry could be put in place for the production of a set number of treatments per

year to be allocated to all countries, according to needs, under an agreement that they would monitor use and restrict utilization to agreed health-care settings (such as secondary or tertiary level hospitals, for example).

This would exclude direct commercialization of the product in private pharmacies and prescription for indications where other therapeutic interventions are available. These conditions would ensure preservation of the new drugs.

6. An intergovernmental consortium to manage distribution and preservation of new antibiotics

This programme would be managed primarily through an intergovernmental consortium which would provide both financing and oversight. Operationalization could be the responsibility of an entity that could be modeled as a non-profit public pharmaceutical company as exists on national level in various countries. This entity would also be responsible for registering the new product in individual countries.

The proposed intergovernmental consortium would have the following four objectives: promotion of innovation, access to all in need, controlled use for better preservation, and inclusiveness.

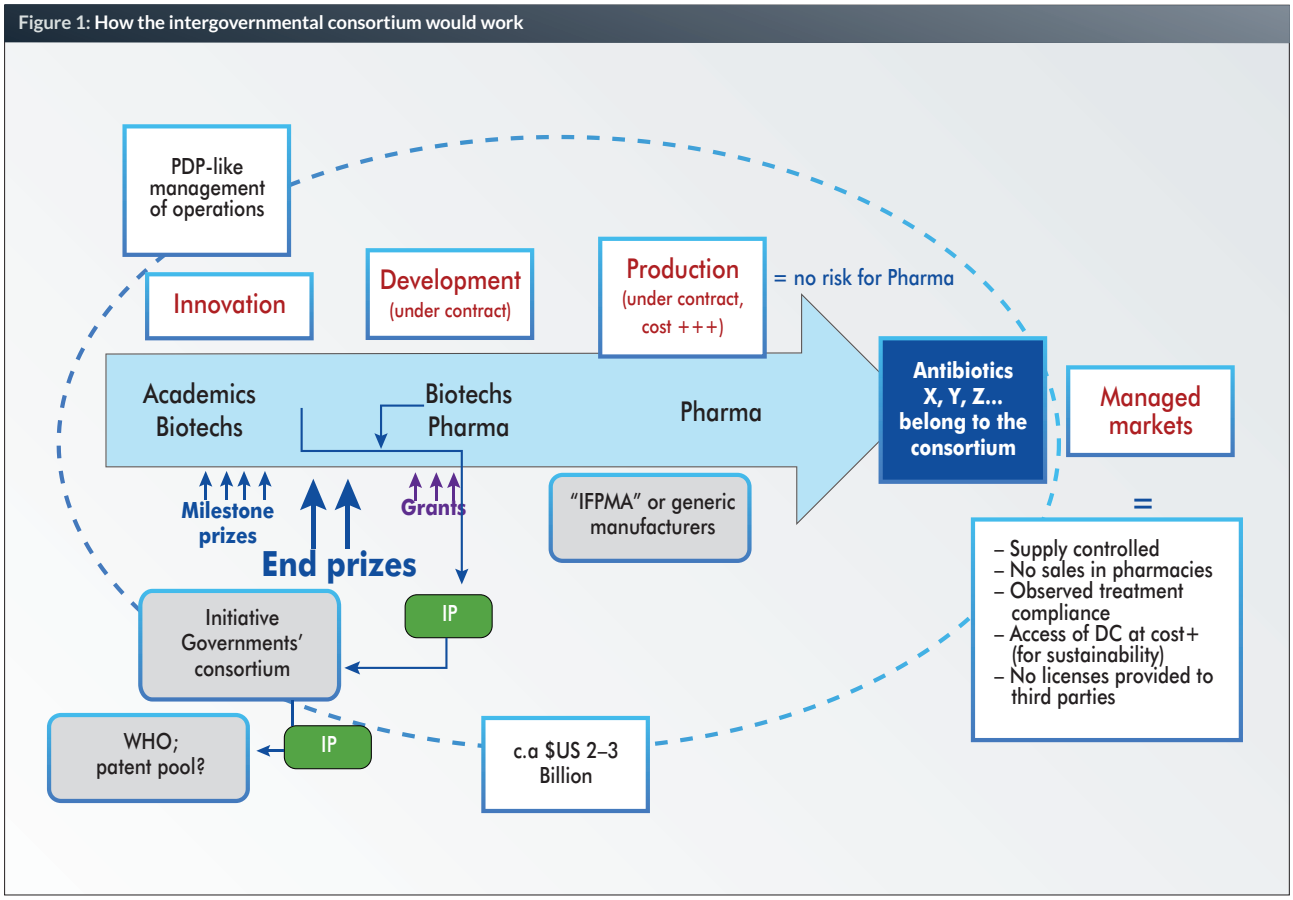
Promotion of innovation:

- Public funding of scientific research should be encouraged. The United States has the largest health research public sector-funding in the world, followed by Western Europe as a whole *(29)*. Having understood the value of research and innovation for economic growth, China is about to catch up and overtake the United States *(30)*. Other countries such as Brazil, Singapore, South Korea and India also have considerable investments in pharmaceutical R&D.
- The framework would increase the potential and the means for fundamental discoveries in new antibiotics, since it would separate basic research funding from clinical trial funding and management (a huge part of the costs of bringing products to the table), as well as from production and marketing costs.
- Grants and prizes would be a crucial asset: the twenty-first century is exploding with scientific and technical capacities, tapping this potential widely and openly would greatly favour fundamental breakthroughs in new antibiotics.

Access to all in need:

- The capacity to prevent disability and death from

Figure 1: How the intergovernmental consortium would work



infectious diseases, everywhere, should be a Global Public Good; all countries would have access to the new antibiotics on a needs-basis at an affordable price under the proposed intergovernmental consortium.

Controlled use for better preservation:

- All partners to the consortium would have to adhere to standards of responsible use to delay the development of resistance. Countries would have to set up national plans for preservation.
- Strict means to control dispensation would be needed at all levels in all countries, including access to latest state of the art diagnostics.
- No licenses would be provided for veterinary use, in order to avoid and the current overuse of antibiotics in the food industry.

Inclusiveness:

- Low-income countries have a lot of potential to contribute to innovation in antibiotics, notably but not solely, by the search for new natural resources or the tapping of traditional knowledge.
- Most discovery and innovative concepts arise in academia and small biotech enterprises. Multinational pharmaceutical companies often buy up small innovating firms or license inventions from universities. Innovations are spurred by scientific freedom, unshackled by demands of short term profitability or bureaucratic oversight.
- Middle-income countries have undergone very fast expansion of their capacities in pharmaceutical research and high-level biotech industry generally; their contribution to any new antibiotic development project would be important *(31)*.

The consortium would be funded by governments and other public sector entities, to which philanthropic foundations could be added. A considerable financial commitment (possibly in tens of US$ billions) over a 15 year period would be needed. The current estimated cost of developing one new drug is between US$ 5 billion *(32)* and 500 million *(33)*.

The core concept here is the need for a type of institution which would enter into a dynamic interplay with the scientific innovative capabilities of the many actors and which would creatively feedback innovative products into society *(34)*.

Finally, "prevention comes first!"

"Prevention first. Every infection prevented is one that needs no treatment!", according to the WHO Draft global action plan on antimicrobial resistance *(35)*. The drive to find and produce new antibiotics should be accompanied with much stronger efforts for prevention than is currently the case, in order to reduce the number of patients who might contract drug resistant infections from the environment, within health systems, and hence need treatments. There is a need for:

- 1- much stronger and more efficient prevention of hospital acquired infections;
- 2- prevention and monitoring to prevent AMR entering the food chain;
- 3- surveillance, monitoring of water and waste, as well as global investments to improve LMICs water and sanitation systems *(36)*.

As the Ebola crisis has demonstrated, there is an urgent need for strong investment in infection prevention and control in the health systems of low-income countries, including in situation where there is no market for advanced technologies in the prevention of in-health centre transmission of infections.

Newer antibiotics would be most efficient in a global environment in which preventative measures had been taken as outlined above, it would give the new drugs a longer life span.

While the drive for antibiotics R&D is most urgent, other research avenues, some which have began to be explored *(37, 38)* others in the wings, should not be forgotten, and some might benefit from some of the options presented here for a newer, more modern R&D model for the common public good of benefit to all. •

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