The World´s Collective Responsibility to Conserve Antibiotic Effectiveness

ReAct
Action on Antibiotic Resistance

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Photo credits

”A world free from fear of untreatable infections”

BACKGROUND

About the "Collective Responsibility for Controlled Distribution and Use" policy process

Having successfully argued for a different business model for research and development (R&D) [1,2], ReAct initiated a debate about how future antibiotics could be distributed and used in a way that would minimize the risk of development of resistance[1]. When new antibiotics are developed, the following questions must be answered:

- What policies must be put in place to minimize the development of antibiotic resistance (ABR)?
- How can we ensure that new antibiotics are made globally accessible and affordable to all those who need them?
- How should new antibiotics be distributed to balance the need for access against the risk of inappropriate use?

This document builds upon the ideas and proposals generated in response to the above questions at two roundtable discussions on "Exploring Ways to Preserve Future Novel Antibiotics", organized by ReAct in the fall of 2011 in New Delhi and in Antalya, Turkey which aimed to begin a global debate on the questions set out above.

ReAct, continues to bring a focus to these questions though its regional work in Europe, Latin America, South East Asia and Africa, at workshops organized by ReAct and its partners and by participating in discussions at different fora.

ABR has caught the attention of many countries and organisations; however, the global response has been slow and uncoordinated. The sense of urgency generated by media coverage of reports and activities must be leveraged for sustainable action.

The complex challenges require harnessing diverse capacities worldwide. ABR is a global problem that requires both local action and solutions and global coordinated responses. The responsibility and leadership rests with all of us.

ReAct now calls for a formal global debate on future distribution and use of new antibiotics with the participation of all stakeholders. WHO, other UN agencies, and national governments should draw up the framework for work to proceed based on new insights and agreements emerging from the debate.

ReAct welcomes reactions and comments to the ideas put forward in this policy document.

[1] Collaboration for Innovation - The Urgent Need for New Antibiotics. ReAct policy seminar, Brussels, 23 May 2011. http://www.reactgroup.org/uploads/resources/Collaboration-for-Innovation-for-webb.pdf

1. INTRODUCTION

Antibiotics: from a magic bullet to an endangered public good

Antibiotics changed the world by saving and improving countless lives. However, their effectiveness is at risk. Increasing ABR and a distressing decline in antibiotic R&D are threatening our ability to treat common infections and the unavoidable infections that come with cancer chemotherapy, organ transplantations or the care of premature babies.

Increasingly, we cannot safely treat multi-drug resistant (MDR) strains of typhoid fever a major killer of children in low and middle-income countries (LMICs) [3], nor MDR gonorrhoea with 106 million new cases per year[2].

ABR is a natural process that results from bacterial adaptation to antibiotic exposure. The problem is fuelled by profligate use of antibiotics in human and veterinary medicine and agriculture coupled to poor sanitation, hygiene and infection control. Intensified human mobility and food trade also accelerate the spread of resistant bacteria.

Environments polluted by antibiotics used in aquaculture and agriculture practices, and by wastewater from municipalities, hospitals and pharmaceutical manufacturing also seem to play a role in ABR development and dissemination [4] . Antibiotic use is highly prevalent and the ways we are using them are affecting not just people but the entire ecosystem.

ABR moves across borders making it a global problem. It is a challenge as all health systems rely on effective antibiotics to treat and prevent infections and countries have to face the inevitable consequence of increase in health care and societal costs. In addition to the obvious need to support sanitation, hygiene, infection prevention and control programs, solutions to tackle ABR must:

- Find the right funding arrangements to re-boot R&D for novel antibiotics that meet current and future medical needs.
- Build a system of surveillance of infections, antibiotic use and antibiotic resistance.
- Determine how the distribution and use of existing and new antibiotics can be better managed to minimize resistance.
- Ensure equitable access for all who need them.
- Facilitate a paradigm shift in the understanding of ABR and the life-style changes that also need to accompany technical solutions.

[2] http://www.who.int/reproductivehealth/publications/rtis/who_rhr_11_14/en/

2. INVIGORATING R&D FOR NEW ANTIBIOTICS

Responding to the steep decline in discovery of novel antibiotics and impending loss of control of infections, governments, scientists and policy groups have called for and proposed various approaches to reinvigorate R&D for antibiotics. Proposals include adoption of new R&D funding (e.g. public-private partnerships (PPP)), new collaborative models, and de-linking investments from sales volumes.

A collaborative 3Rs model encompasses sharing of Resources (e.g. research inputs from private and the academic sectors), Risks (e.g. of research and development across public and private sectors) and Rewards (e.g. conditional public funding providing fair returns on R&D, public buyout of patents etc.) [5].

The concept of de-linkage offers a necessary alternative to the traditional business model if the return on investment is not to be tied to volume-based sales, and if the economic incentive to sell more -that runs counters to conserving antibiotics- is to be severed. Other de-linkage models put forward are being considered by various groups and organisations including WHO[3].

Regulatory changes have also been proposed to allow approval of new antimicrobials based on small, low-cost clinical trials for infections where insufficient therapeutic options exist [6] .

The initiatives to stimulate antibiotic R&D currently in place use very different approaches. In the US, the Generating Antibiotics Incentives Now (GAIN) Act of 2011 provides an extension of data exclusivity by five years, and designates qualified infectious disease products to be eligible for a fast track system among other provisions for breakthrough drugs including antibiotics[4].

However, time discounting for extended data exclusivity will have little, if any, economic effect. The GAIN Act has been making it easier for analogues of existing drugs to come to market with longer periods of monopoly protection, thereby worsening therapeutic competition and lowering the potential net present value for truly novel antibiotics when they come to market.

In Europe, the program "New Drugs for Bad Bugs" (ND4BB) is being implemented through the Innovative Medicine Initiative (IMI), a PPP between the European Federation of Pharmaceutical Industries and Associations and the European Union[5]. The European Gram-negative Antibacterial Engine (ENABLE) project[6], a project within the "New Drugs for Bad Bugs

3 Outterson K. – New Business Models for Sustainable Antibiotics. Working Groups on Antimicrobial Resistance. Prepared for Centre on Global Health Security Working Group Papers. Chatham House Feb 2014. http://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0214SustainableAntibiotics.pdf
4 http://www.pewhealth.org/uploadedFiles/PHG/Supporting_Items/IB_FS_Antibiotics_GAIN_BIll_Summary.pdf
5 http://www.efpia.eu/topics/innovation/innovative-medicines-initiative
6 http://www.imi.europa.eu/content/enable

(ND4BB)" IMI programme, involves 32 participating partners spanning 13 countries with the objective "to establish a significant anti-bacterial drug discovery platform for the progression of research programmes through discovery and Phase 1 clinical trials".

The plan is to create a full development pipeline, through opening up the programme to others with the goal of delivering "at least one novel anti-bacterial candidate against gram negative infections into Phase 2 clinical trials by 2019". For PPPs developing new antibiotics in general, and the IMI ND4BB in particular, intellectual property (IP) issues need to be resolved and defined to ensure affordability and access of the antibiotics that are developed under the PPP. When public money is used, agreements need to be open and transparent.

None of these initiatives take a comprehensive view of the whole value chain including how future antibiotics, once developed, will be distributed and used to minimize the risk of resistance development. A particular concern voiced about the GAIN Act and its extended data exclusivity is that it does not offer a departure from the traditional market model or offer any insights into how this arrangement can contribute to rational use of new antibiotics.

Whatever policies are used to solve the lack of innovation, they must foster development of antibiotics with a novel mechanism of action, be based on a public health needs analysis that takes into account surveillance data on resistance, and consider the question of global access at affordable prices. R&D and advocacy for diagnostic tools that can accurately differentiate bacterial from viral infection and, ideally, indicate the correct antibiotic treatment must be also considered and deserve investments.

A global forum to debate these concerns, including regulatory incentives for the development and preservation of novel antibiotics and the need to develop new, affordable and quick diagnostic tools, especially for use in low- and middle-income countries (LMICs) is needed. Physicians, academia, WHO, Civil Society Organisations (CSOs), diagnostic manufacturers and others need to contribute to the process of specifying criteria for the most urgently diagnostic tools.

3. CONSERVING EXISTING AND FUTURE ANTIBIOTICS

3.1 Underpinning principles for a new framework for establishing new policies and norms for antibiotics

To conserve existing and new antibiotics, ideally, they should be:

- correctly selected based on medical needs and local surveillance data;
- supported by accurate and rapid diagnosis;
- dispensed and sold with care and advice;
- used properly for maximum effectiveness and minimum contribution to ABR;
- accessible to people who need them, and affordable at both national and local levels;
- tightly controlled in their journey from manufacturer to patient, without promotional or financial incentives that influence decisions of health workers and consumers; and
- prevented from being falsified.

A radical re-think of current policies and establishing new norms of antibiotic use is critical to avoid humanity losing control of the ability to manage infections. Such norms should be based on the following principles:

- *effective antibiotics are an essential public good* that must be available to all in need in a timely and affordable manner;
- protecting antibiotics and containing ABR is a *collective responsibility;*
- *prevention of infection* requires addressing gaps in sanitation, infection control, vaccination, and nutrition; and
- addressing ABR requires an *ecosystem approach* given the dynamic nature of the human host-microbe interaction and the interconnectedness and environmental impact of antibiotic use in humans, animals and food production.

3.2 Core components for conserving antibiotics

3.2.1 Strengthening Surveillance - linking national antibiotic needs and individual prescribing decisions to local ABR patterns

Systems for infection surveillance and reporting on antibiotic use and ABR are the bedrock of decision-making on national needs and treatment guidance. Improved local monitoring, resistance data collection and surveillance of antibiotic use will enhance optimizing the use of current and future antibiotics in the following ways:

- Detecting and providing early warning of new resistance and identifying areas for intervention and monitoring.
- Underpinning local treatment guidelines.
- Providing information for cost-of- illness/burden assessment.
- Guiding needs-driven R&D for new antibiotics.

However, many countries have limited surveillance capacity and the current information on ABR burden is inadequate, unreliable, patchy, and mostly drawn from data that is hospital rather than population-based. According to the WHO Global Report on AMR surveillance 2014[7], surveillance of ABR is neither coordinated nor harmonized and there are many gaps in information on bacteria of major public health importance.

Global country by country maps of antibiotic use and resistance based on each country's local surveillance data should be developed to inform decision making, monitor trends and impact of interventions and to benchmark country performance in tackling ABR.
It is therefore essential to build, lift up and revamp surveillance systems and surveillance capacity.

Moreover, there is a need to decide which forms of ABR should be reported by individual countries and whether the current International Health Regulations are the best instrument for collecting and disseminating information.

7 http://www.who.int/drugresistance/documents/surveillancereport/en/

Countries and organizations with expertise and capacity must work with and assist the WHO on building country abilities and a global surveillance system across human and animal sectors, including identification of resources (financial and technical) needed to develop a comprehensive surveillance system in LICs and LMICs.

Surveillance must be embedded as an integral component of all global health programs where antibiotics are provided. Antibiotics are a key element of the Global Action Plan for Pneumonia and Diarrhoea[8] and Save the Children's campaign "State of the World 's Mothers –Surviving the first day[9].

However, these global initiatives do not directly consider strengthening/building up surveillance capacity to ensure that the recommended antibiotics are effective. Thus, existing global health programs in which antibiotics are a component must concurrently build in and fund mechanisms to develop surveillance capacity in order to ensure the effectiveness of antibiotics provided. This capacity should contribute to the building of a global surveillance system.

3.2.2 Promoting Rational prescribing and use

(i) Identify and take into account what influences prescribing and use of antibiotics.

Cultural and social values influence people's perceptions, judgement, communication and behaviour, and define how people view illness and healing [7,8]. This has implications on whether interventions that might work in, for example, Western societies have transferable potential when applied to different parts of the world [9] .
Hence, identifying and considering factors and social norms that influence health professionals/workers and consumer behaviour in a given context are imperative for changing inappropriate practices and for creating and seeking support for new ones [10,11].

They include but are not limited to

- Predisposing factors such as beliefs, knowledge (individuals and the community), fear of infection, education level, prior experience, diagnostic uncertainty.
- Reinforcing factors - patient demand, fee-for service structure, social approval, mutual recognition, peer pressure, and drug promotion.
- Regulatory, policy and market incentives.

(ii) Develop interventions that are sustainable

In community and private health care settings, the dynamics between prescribers and consumers are a significant factor in driving antibiotic use. Developing interventions that lead to sustainable change is challenging, time and resource consuming, but a necessary process.

8 http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/
9 http://www.savethechildren.org/atf/cf/%7B9def2ebe-10ae-432c-9bd0-df91d2eba74a%7D/SOWM-FULL-REPORT_2013.PDF

Interventions to promote good practices among prescribers and users include restricting or approving treatment choice and alternatives based on decision-making algorithms with monitoring and feedback.

Successful interventions consider local contexts, engage relevant stakeholders and employ an approach that adopts iterative processes of design, testing, implementation, monitoring and review. Encouraging examples that take these factors into account include a web-based intervention to reduce antibiotic prescribing for acute cough in multiple European countries [12], and the Antibiotic Smart Use Program (ASU) in Thailand [13].

They incorporate interactive educational methods, correct sub-optimal prescribing behaviour, and consider patient education and satisfaction of clinical outcome.

Simply providing treatment guidelines, especially in community settings, is not adequate. Strategies that incorporate a supportive decision-making component through teaching communication/ negotiation skills with opportunities for prescribers to reflect, discuss, and share experiences on their practice with their peers, have been found to reduce antibiotic prescription [14,15].

Public campaigns and peer processes to change expectations through informing, educating and raising awareness and that reinforces prescribers and pharmacist's advice result in less demand for antibiotics. A Cochrane review that evaluated studies conducted in 17 HICs and 2 middle-income countries (MICs) found no significant differences between persuasive and restrictive interventions although restrictive interventions led to more immediate effect [16] .

By and large, the most effective interventions involved providers in the design and evaluation. The review highlighted the lack of standardization in studies as a major challenge for carrying out comparative analysis.

It is crucial to generate evidence at community level and to leverage support from academia, health insurance and government sectors for scaling up interventions and for creating new norms of behaviour. An international system for sharing interventions, focusing on antibiotics, should be established to support country initiatives.

(iii) Develop and implement antibiotic stewardship programmes (ASPs)

ASPs are effective in changing the prescribing behaviour for benefit of greater number of patients, for example in hospitals and in long-term care facilities[16]. Often included as part of healthcare safety and quality goals, ASP are also mandated as part of hospital accreditation process in many countries[10]. A variety of ASP models can be considered depending on hospital budget and size of operation [17,18].

The reach of the programs can be multiplied when they are introduced by legislation covering all public hospitals as in the State of California, or when the entire country participates as in the Swedish STRAMA program (Strategic Programme for the Rational Use of Antimicrobial Agents)[11].

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[10] Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). Antimicrobial Stewardship: 'Start Smart—Then Focus'. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/146981/dh_131181.pdf.pdf.

[11] http://en.strama.se/dyn/,84,,.html

Supporting the introduction of ASPs can be realised through bilateral programs – an example is the cooperation between Vietnam and UK in developing a national antimicrobial stewardship programme for the country [19,20]. Governments should encourage hospitals and long-term care facilities to adopt ASPs by offering incentives or penalties for non-compliance. Ideally, ASPs should link all health system levels bridging hospitals to community health care providers.

WHO should encourage all countries to adopt a national plan on rational use of antibiotics and take action to implement it. In order to do so, LMIC countries should be supported financially and technically, including via capacity building, to enable them to effectively implement the plan.

3.2.3 Solving scientific gaps in optimal antibiotic therapy

Strategies to conserve antibiotics must also address major knowledge gaps on what constitutes an optimal treatment regimen. WHO should take the lead, and together with other stakeholders, decide a process to prioritize research questions that need to be answered and design a process by which countries contribute to answering them. Public funding needs to be available for studies on the optimal dose, dosage regimen and length of treatment to minimize resistance development.

The serious lack of new antibiotics in the pipeline to treat multi-resistant bacteria also warrants studies on the effects of combination therapies. Strategies should include clear therapeutic guidelines as part of broader ASP. Importantly, increase in prescriber's confidence and acceptance seems to play a role in sustaining a new norm [12,13]. Many of these strategies are not realistic options in countries with inadequate access to antibiotics and laboratory diagnostics. Strategies tailored to different contexts must be developed and adopted.

3.2.4 Dispensing and selling with care and advice: role of pharmacists and private drug sellers

Pharmacists play a critical role in the management of medicines for patients and are in a good position to carry out patient education on self-limiting illnesses and to provide self-care treatments that reduce visits to doctors and avoid unnecessary use of antibiotics.

Pharmacists are in a unique position to meet the changing public health needs in LMICs where there is a critical shortage of doctors and other health care providers.

However, in order to do so, they need to re-assess their role to better meet the needs of communities using their knowledge and skill sets in pharmaceutical management. They are urged to examine their role, raise standards and make the profession more relevant to the needs of the public and the health system [21] .

In many LICs and MICs, drug sellers fill the void of doctors and pharmacists. Because of their accessibility as sole providers of medicines in remote areas, educational interventions have been developed and implemented in attempts to raise the standards and add value to drug sellers' activities in some in African countries.

Although these have produced mixed results [22,23], disappointing outcomes should not discourage continuing efforts to fine-tune such interventions. Meeting the public access needs in rural and urban areas of LICs may warrant different standards of practice and regulatory requirements [24].

Providing incentives (tax breaks, scholarships, housing subsidies) may foster an environment for drug sellers to operate and meet the needs of remote communities that ought to be discussed with regulators and the communities that the drug sellers serve [25] . Supporting investments to upgrade drug sellers' skills and motivation for community safety is thus commendable. Pharmacists' professional organizations in partnership with ministries of health can assist in extending the skills to drug sellers offering a path to semi-professionalization.

3.2.5 Ban routine antibiotic prophylaxis and antibiotics used for growth promotion in animal husbandry, agriculture an aquaculture

Antibiotic use in food production poses risks to human health. Animals are treated with antibiotics both for curing disease and promoting growth [26] , fruit trees are [27] frequently treated prophylactically with antibiotics to control bacterial infections , and aquaculture relies on antibiotics to manage infectious disease [28] . The effect of these practices extends beyond the site of use contributing to environmental contamination, ABR development and dissemination.

The Codex Alimentarius Commission, jointly established by the WHO and FAO, has recognized the adverse implications of ABR for human health and for international trade. 'Code of Practice to Minimize and Contain Antimicrobial Resistance' (CAC/RCP 61-2005) and 'Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance' (CAC/GL 77-2011) have been developed for countries to use in regulating their own food safety control but on a voluntary basis [29] .

The WHO Advisory Group on Integrated Surveillance Antimicrobial Resistance (AGISAR) has recommended that the use of critically important antibiotics must be restricted to use in humans and not for food production. AGISAR has also called for surveillance/monitoring of usage and resistance of antibiotics in food production[12].

Member countries should seriously consider the applicability of these guidelines, and seek assistance when needed. An agreement to require all countries to do so would facilitate this.

Sweden banned the use of antibiotics as growth promoters in 1986. The EU initiated a gradual restricted authorization of the use of antibiotics for growth promotion in the 1990's; use was finally banned in 2006. In contrast to the EU, the US Food and Drug Administration (FDA) did not opt for a ban or set target goals for reduction but in 2013 issued voluntary guidelines for use of antimicrobials in food production

12 Report of the 3rd meeting of the WHO advisory group on integrated surveillance of antimicrobial resistance, 14-17 June 2011, Oslo, Norway. AGISAR 3. http://www.who.int/foodborne_disease/resistance/agisar_june11/en/.

and the rearing of animals[13]. Whether the call for adoption of recommendations in the guidance and judicious use will reduce the use of antibiotics as growth promoters remains to be seen.

Steps taken to regulate the use of the antibiotics in livestock that are medically important for humans have not shown to have a negative impact on the industry (e.g. some European countries [30] and Australia [31]). On the broader ecosystem front, countries should adopt the concept that underpins the One Health Initiative[14] to guide the reduction of risks of infectious diseases at the animal-human interface.

Taking into consideration these risks, and with the aim to preserve the effectiveness of antibiotics, new and old classes of antibiotics critical to human health should be exclusively reserved for humans. Moreover, antibiotic use for growth promotion and mass disease prevention as a substitute for poor husbandry and animal welfare must be prohibited.

3.2.6 Ban commercial advertising of antibiotics

Active marketing strategies employed by pharmaceutical companies to recoup their R&D investments through high sales volumes is both counterproductive for the goal of conserving antibiotics and reducing resistance, and against the spirit of public investments.

Other forms of marketing such as direct-to-consumer-advertising (DTCA) are also a source of concern. In US and New Zealand where DTCA is legal, advertising of prescription medicines is linked to less appropriate prescribing, increase in patient demand and shifts in prescribing to newer and more expensive drugs [32]. Contrary to arguments supporting DTCA, they do not educate the public about diseases or drugs [33].

Given the influence that marketing activities have on prescribers and users, it is reasonable to propose that regulators and the pharmaceutical industry give serious consideration to a moratorium on commercial advertising activities for existing and new antibiotics. Such a proposal gains more traction considering the nature of antibiotics as a global public good and when public investments are made for R&D efforts.

All advertising from Internet to drug sellers should be covered under such a moratorium. In their place, independent and unbiased sources of education and

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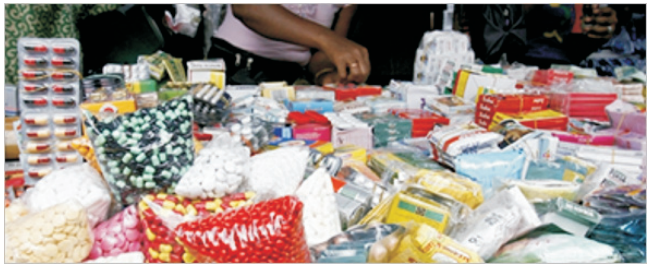
[13] FDA takes significant steps to address antimicrobial resistance. Agency implementing plan to ensure judicious use of antibiotics in food animals. FDA News Release. December 11, 2013. //www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm378193.htm,
NRDC Press Release. December 11, 2013. FDA's New Antibiotics Policy Fails to Protect Health. NRDC: FDA Gives Industry a Free Pass on Antibiotic Misuse. http://www.nrdc.org/media/2013/131211.asp,
Health Food Action. FDA Underwhelms with Response to Super-Resistant Infections Rise. Posted on December 31, 2013. http://healthyfoodaction.org/fda-underwhelms-with-response-to-super-resistant-infections-rise/.

[14] One Health Initiative was established as One Health One World – a strategic framework for reducing risks of infectious diseases at the animal-human-ecosystem interface by FAO, who, OIE, UNICEF, the World Bank and UNSICHAS. http://www.onehealthinitiative.com/

information developed by relevant health professions and their societies should be available to all health professionals and consumers using strategies found to be effective (see Section 3.2) [32, 33] . CSOs and health professional groups should lead the work towards drafting principles to underpin country legislation including penalties for violation at country level and additional penalties for companies at global level.

3.2.7 Falsified and substandard antibiotics: Contributing factors to treatment failure and ABR

Antibiotics are the most counterfeited medicines, accounting for 28% of global counterfeit medicines [34] They are more prevalent in regions with weak regulatory oversight and high burden of infections. While national drugs regulatory authorities are responsible for the safety of a country's drug supply, no single country can entirely guarantee this today.



Over the years, many attempts have been made to address this problem but lack of consensus on terminology and conflation with intellectual property has stymied progress. The legal instrument that is currently available is the Council of Europe Convention (MediCrime Convention)[15] with only one country ratifying the convention to date.

The US Institute of Medicine recommends strengthening regulatory oversight, and highlights the need to improve pharmaceutical supply chain security as well as detection technology solutions [25]. Its preferred option is the "soft law" approach and recommended the development of a "code of practice on the global problem of falsified and substandard medicines". But compliance to the code or ratifying conventions requires willingness and ability of countries to do so.

Further, the code, modelled on the International Code of Breast-milk Substitutes, would require setting up of global monitoring and reporting arms to make it feasible. Others have advocated for a global treaty that combines legal, technical and financial aspects and referred to precedents established to tackle counterfeit banknotes, tobacco control and the environment and their applicability to falsified medicines [29].

A process to resolve opposing views on whether to use non-legally binding guidelines and policies, or a global treaty would help move the debate forward.

Regardless of different views and proposed solutions, countries need support to attain a robust and rigorous regulatory system, and access to technology to detect falsified or substandard medicines. A recent study that evaluated the affordability and suitability of 42 detection devices for use in LICs and MICs suggests that government and private aid agencies who are already importing and distributing medicines for their health programmes can help by absorbing the costs of these devices [35].

It is essential to develop or extend existing networking systems on a global scale to alert regulatory agencies,

15 Council of Europe. Convention on the counterfeiting of medical products and similar crimes involving threats to public health. 2011. http://conventions.coe.int/Treaty/EN/Treaties/Html/211.htm.

RWANDA: LEGAL AND TECHNICAL APPROACH TO DRUG QUALITY

- Late 1990's - Rwanda mandated that all drug contracts awarded by the Ministry of Health must be to manufacturers with WHO-approved certificates of Good Manufacturing Practices.
- 2011 - Formed pharmacovigilance sub-committees at all 469 health centers that are overseen by the country's 42 district hospitals. 2,400 health workers and more have been trained in the implementation of the guidelines.
- Accredited private sector integrated with public sector supply hain on medicines for high priority diseases.
- Agencies involved for inspection, testing and legal actions – Bureau of Standards, Customs Services Department, Ministry of Health, Rwandan police force and Interpol.
- Working with East African Community in drafting regional law

Binagwaho A, Bate R, Gasana M, Karema C, Mucyo Y, et al. (2013) Combatting Substandard and Falsified Medicines: A View from Rwanda. PLoS Med 10(7): e1001476. doi:10.1371/journal.pmed.1001476r.

procurement agencies and consumers about falsified and substandard antibiotics.

Decisive actions are needed by WHO and other organizations with technical and legal expertise to advance an offensive against this onerous multifaceted problem.

3.3. Striking a balance between access and excess: a new framework for achieving equity of access

There are huge disparities in access to antibiotics globally. Countries have different capacities and policy options to guarantee antibiotic access whilst deterring excess. Balancing access and excess requires reconceptualization of all components of the pharmaceutical value chain.

Much also relies on the robustness of health systems (HS) including pharmaceutical supply chains, effective drug regulatory and data systems, treatment and policy guidelines, and financing arrangements.

There is a compelling case for striking a balance in the access/excess because antibiotics constitute a special class of medicines; they must be considered a non-renewable resource whose use by any individual impacts the current and future health of both the individual and the population [36] .

However, the path to balancing access and excess is strewn with financial, structural and geographical obstacles particularly in LICs and in many parts of MICs. Financial limitations are found at both public and individual level preventing access to needed

antibiotics. Perverse financial incentives (e.g. where hospital income and/or doctors' income is derived from sale of medicines) that undermine patients' best interest also contribute to unnecessary and excessive use [37]. Financial constraints may lead to purchasing inappropriate antibiotics based on price alone or lead to misuse where an antibiotic course is not completed but saved for future use.

3.3.1 Use regulations and policies

Actions to control access and prevent excess while ensuring affordability comprise regulatory, policy and financing options which can include: (i) classifying new and existing antibiotics as a special medicine category and limiting prescribing to defined health system levels; (ii) requiring potential for resistance with respect to projected use in efficacy and safety assessment criteria; (iii) applying resistance risk as a criterion for selection of and subsidized access to antibiotics by public and private insurance schemes; and (iv) developing new models for affordability at country and individual level.

On the regulatory and policy side, there is a role for both the International Conference of Drug Regulatory Authorities and the International Conference on Harmonization to provide regulatory expertise and provide a forum for global agreements. Evaluations should be conducted on how prospective regulations impact people's access, particularly in countries with complex and challenging supply systems where antibiotics are normally sold over-the-counter (OTC).

A pragmatic roadmap for combating ABR developed by Indian medical societies in the Chennai Declaration considers options ranging from imposing restrictions on certain classes of antibiotics to accepting OTC sales [38].

3.3.2 Last mile challenge

Many countries face enormous structural and geographical obstacles in ensuring effective delivery of antibiotics from manufacturers and importers to the end users. Complex and complicated distribution arrangements contribute to unreliable delivery of needed antibiotics. Solutions for improving their access must draw from lessons and experiences from programmes that deliver medicines for e.g. HIV/AIDS, tuberculosis, malaria and other neglected diseases. A recent finding on the dominant role that wholesalers play in determining access to antimalarial drugs illustrates the need to engage them in designing delivery strategies [39] .

The “last mile-challenge” needs solid commitment and innovative approaches to build workable pathways if all in need are to have affordable reliable access to effective antibiotics. Unfortunately, existing efforts, both using tracking technologies and borrowing from the practices of the supply of consumer goods such as Coca Cola, mainly address logistics without concomitant strategies to promote rational use and proper surveillance.

Possible solutions to provide access in remote areas but within a controlled framework may lie in existing programmes such as integrated community case management (ICCM). In ICCM, community members, health workers or nurses are trained to identify and provide treatment in communities with little access to health. ICCM has increased access to treatment for childhood illnesses including antibiotics for pneumonia reducing infant mortality rates.

The concept of extending ICCM as part of public health structure and systems offers a model for the delivery of antibiotics where necessary. Adding

diagnostic tools as part of tools for commonly seen illnesses and infections may lead to successful pathways to access needed antibiotics.

3.3.3. Make the price right

A novel and workable pricing system is needed to ensure that antibiotics are affordable and accessible to LICs and LMICs. Current pricing strategies such as tiered pricing and market segmentation do not necessarily guarantee affordability especially for the poor and those who pay out of pocket. Generally, competition among suppliers should provide the lowest prices, but this competition has to be properly harnessed and monitored [41]. Principles elucidated in section 3.1 that defined effective antibiotics as an essential public good to be available to those who need them in timely and affordable manner should underpin the pricing models.

The R&D incentives now in place may result in pricing agreements with worldwide affordability implications. Hence, pricing models should be developed for discussion and agreed upon well before novel antibiotics reach the end phase of R&D.

A 5-YEAR PRAGMATIC PLAN BY INDIAN MEDICAL SOCIETIES

- A pragmatic roadmap for combating ABR developed by Indian medical societies in the Chennai Declaration considers options ranging from imposing restrictions on certain classes of antibiotics to accepting OTC sales.
- Recently, the participants of the Chennai Declaration, keeping with its pragmatic "Practical not Perfect" approach prepared realistic, achievable targets for 1st, 2nd and 5 year marks.
- They address antibiotic stewardship, infection control, OTC sale of antibiotics for humans and animals, private-public partnership to develop new molecules,medical education and improving laboratory capabilities.
- The role of NGOs and the media are also covered.

Team C. "Chennai Declaration" : 5-year plan to tackle the challenge of anti-microbial resistance. Indian J Med Microbiol 0;1:7.

4. HARNESSING GLOBAL LEADERSHIP

The World Economic Forum identified ABR as the "greatest risk to human health" underscoring the importance of collective and urgent action including the estimation of human, social and economic costs [42].

National and regional responses and commitments to contain and de-escalate ABR seen across the globe demonstrate growing awareness and recognition. This momentum must be seized to further mainstream new antibiotic norms and ABR into national, regional and global health, security, research and development agendas.

Containment of ABR depends on engagement at all levels, from individuals, households and the communities, to health care facilities, the entire health

sector, and finally to national and global levels [43] .The push for Universal Health Coverage (UHC) and calls for health systems strengthening (HSS) offer opportunities to leverage changes to contain ABR.

Equitable access to new antibiotics, their controlled distribution and rational use must be mainstreamed and embedded into all UHC reforms being considered by many countries as part of the new global health agenda [44]. The availability of effective antibiotics needs to be seen from a health system's perspective and consider the social and economic determinants of infectious diseases. The role of CSOs in ensuring the realization of this goal cannot be overstated.

Antibiotics are one of 13 life-saving commodities (UN commission), and a crucial component of major health initiatives[16]. The lack of effective antibiotics undermines the achievements of the MDGs and jeopardizes what has been achieved so far[17]. On the other hand, ABR could provide a practical focus for achieving global health goals post-2015, serving as a tool to track implementation and integration of national medicines policies into health systems as done in Thailand and Brazil.

UNESCO and The World Academy of Sciences should use their agenda-setting power to call for the education of lay populations and for inclusion in health sciences curricula and teaching on the need to conserve antibiotics. Education of health professionals and health workers about ABR and rational prescribing should be mainstreamed in all training programs. Health professional champions and patient and consumer organizations must educate their respective members about ABR and appropriate use of antibiotics. Community and patient empowerment and participation in all aspects of intervention programs are essential to develop and advocate innovative ideas that can capture the potential of communities for learning and teaching.

A parallel to climate change may be drawn. Recent research suggests that to prompt collective action, uncertainty about when danger will occur needs be reduced [45]. Thus, predicting and communicating the tipping point for antibiotic failure with greater certainty, if at all possible, might facilitate stronger collective and collaborative international action.

5. TIME FOR DEBATE IS OVER

In the crowded arena of global health issues, growing ABR, access to needed antibiotics and rational use demand the world's attention. ABR is a potential personal and societal risk not limited to a group of people or a disease, affirming its place as a cross cutting issue for post-2015 goals, UHC and HSS.

ABR is a clear inter-sectorial, trans-national and cross-governmental issue. The numbers of hard-to-treat and untreatable infections are growing. WHO and health leaders of regional political and economic bodies, individual countries and scientific organizations have called for action.

So what are we waiting for?

16 UN Commission on Life-Saving Commodities. http://www.everywomaneverychild.org/resources/un-commission-on-life-saving-commodities.
http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/
http://www.savethechildren.org/atf/cf/%7B9def2ebe-10ae-432c-9bd0-df91d2eba74a%7D/SOWM-FULL-REPORT_2013.PDF

17 http://www.reactgroup.org/news/238/18.html

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ACTION ON ANTIBIOTIC RESISTANCE

ReAct, a network dedicated to mobilizing global action on antibiotic resistance, was born in 2004 following a meeting of concerned health professionals, scientists and health activists in Uppsala, Sweden, organized by the Swedish Strategic Program against Antibiotic Resistance (STRAMA), Karolinska Institutet and the Dag Hammarskjöld Foundation.

ReAct focuses its work on fostering innovation, raising public awareness, bridging the evidence gap and uncovering the paradigm shift in the understanding of ABR.

The knowledge and insight gained from its work across these different areas has created a foundation for evolution of a variety of programs seeking innovative and sustainable solutions to deal with what is a complex problem.

ReAct is a global network with presence in Europe Africa, Asia, Australia, Latin America, and North America.

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