Achieving Global Targets for Antimicrobial Resistance

The UN should promote targets, funding, and governance

OVERLINE

Achieving Global Targets for Antimicrobial Resistance

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After decades of neglect, antimicrobial resistance (AMR) has captured the attention and concern of the public health community and global leaders. In September 2016, a high-level meeting of the United Nations General Assembly (UNGA) will discuss how countries can cooperate to preserve global access to effective antimicrobials. This will be only the third health issue (and the first One Health issue, integrating human, animal and environmental health) to bring together heads of state at the UNGA. This is a rare opportunity to set a global agenda to combat the crisis. We believe that (i) setting targets for reducing drug resistant infections, (ii) adequate financing for global action, and (iii) defining the global health architecture to address AMR, should be key elements of a UN plan.

The cost of antibiotic treatment and mortality due to resistance is increasing worldwide (*2*). The greatest burden occurs in low- and middle-income countries (LMICs), especially among the young: an estimated 214,000 neonatal sepsis deaths are attributable to resistant pathogens each year (*7*). But high-income countries are not immune: an estimated 23,000 people in the United States and 25,000 in Europe die each year from resistant pathogens (*2,7*).

That said, lack of access and delayed access to antibiotics kill more people than AMR. The challenge of expanding appropriate access to antimicrobials, while restricting inappropriate access, requires new approaches to financing and delivering healthcare. A One Health perspective can address connections between antimicrobial use and resistance in humans, animals and the wider environment.

Targets and Surveillance

Use of antibiotics is the most important driver of selection for resistance and loss of effectiveness. Use is increasing globally, driven by rising incomes and increasing access. Antibiotic use varies greatly in human and animal sectors across countries, depending on prevailing medical, veterinary and regulatory practices.

We propose that no country consume more than the current median global level (22 standard units per capita per year). We estimate that this would lower overall use by 21% globally (based on (*8*); see supplemental material (SM)). Reducing use is accomplished by improving public health and sanitation. In low-income countries, antibiotics are used to compensate for the lack of public health infrastructure (e.g., vaccination coverage, infection control). A target linked to UN Sustainable Development Goals 3 (on health) and 6 (on water and sanitation) that commits nations to improving public health would reduce reliance on antibiotics.

Further reductions could be achieved through public campaigns, aimed at physicians and patients, to discourage inappropriate antibiotic use (*9*), particularly in response to seasonal influenza (*8*). Though LMICs face a higher burden of infectious disease, per capita consumption of antimicrobials in most LMICs is well below our target level. Thus, meeting this target need not compromise legitimate uses.

There is significant potential for reducing consumption in the animal sector. We propose complete global phase out of use of antimicrobial growth promoters; five years would be appropriate given the urgency of the problem. This could avert much of the projected 67% increase in farm animal use between 2010 and 2030 (*8*). Though this would incur some cost to agricultural sectors, even in China (the largest consumer of antibiotics in agriculture), that cost is likely on the order of $3 billion a year, ~~to be~~ a small fraction of the country's burden of AMR (*10*). ~~Moreover, T~~the costs of improving biosafety and biosecurity in farming operations to phase out antimicrobial growth promoters would be largely offset by lowering risk of infection and cost of antimicrobials. We envision a process similar to that in the EU where there was declared intent to phase out sub-therapeutic use followed by regulatory changes to make the transition ~~it happen.~~ Globally, ~~This~~ this would happen could work through a multilateral process, as with global movements to phase out, e.g., asbestos or chlorofluorocarbons~~.~~

National-level r~~R~~estrictions on antibiotic effluents from pharmaceutical manufacturing, agricultural operations and hospital waste that end up in waterways and contribute to the buildup of resistance genes in the soil and water are an urgent priority.

~~While setting t~~Targets for reductions in antibiotic consumption ~~is important~~should be accompanied by~~, outcome-based targets are critical to assess progress against the ultimate goal of reducing drug-resistant infections. We propose~~ targets ~~be set~~ to reduce levels of a drug resistance index (e.g., the proportion of infections that are resistant), based on weighted-aver~~r~~age of resistance of the eight World Health Organization (WHO) priority pathogens to first line antibiotics, nationally, regionally and globally within 5 years (*10a*). ~~Reductions should be relative to 2016 levels, based on the eight World Health Organization (WHO) priority pathogens.~~ We do not specify the scale of reduction – the immediate priority is to prevent increases – but recommend a review ~~after 5 years~~in 2021 to consider more stringent targets. The ~~weighting given to each drug, and~~ strategies chosen ~~,~~ would reflect ~~usage~~ health system context and priorities of individual countries.

Existing surveillance programs for AMR can contribute to target monitoring at the national level (11), including the Global Antimicrobial Resistance Surveillance System, and ResistanceMap (*12*). Surveillance should involve the livestock sector and the wider environment, and track access and use, and indicators such as water, sanitation, and vaccination coverage. Data on AMR must be translated into epidemiologically sound estimates of public health burden, which requires information on treatment rates and failures (*7*) not routinely collected at present.

Surveillance cannot be the sole responsibility of individual countries; surveillance is a global good and should be financed accordingly. Initiatives such as the Fleming Fund and the Global Health Security Agenda

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provide opportunities to strengthen surveillance in countries with poor public health architecture. Not all surveillance elements need to be replicated at a national level; integrating local activities into multi-national networks may be more efficient, with appropriate structures for data sharing, analysis and communication.

Global financing

Substantial funds have been committed in the U.S. and Europe to tackle AMR, but success will be limited without global scale investments. The need to incentivize development of new vaccines, diagnostics, novel therapies and stewardship methods, as well as traditional antibiotics to ensure availability of the "antibiotic umbrella" has been widely recognized (*13*). Vaccines, for animals and humans, face high development costs and uncertain markets; however, the GAVI Vaccine Alliance financing mechanism has been successful in bringing new vaccines into wide use.

Development and deployment of diagnostics is more difficult. Knowledge of the underlying pathogen and its drug sensitivity would improve antibiotic use, but new diagnostics are needed. Diagnostics must be rapid and sufficiently inexpensive if they are to be used prior to the decision to begin antibiotic treatment. The Longitude, Horizon and NIAID prizes for innovative diagnostics stipulate that winners demonstrate the feasibility of deploying globally.

Novel alternatives to traditional antibiotics are needed. Multiple non-compound approaches that target bacteria or the host have been proposed (*14*). Antibiotics can interact to synergize, antagonize, or suppress each other's effects (*15*), modifying the evolution of resistance.

Financial stimuli for antibiotic development must address the lack of incentives for appropriate use (*16*) and should enable sustainable access, when clinically appropriate. ~~There are proposals for delinkage where the pharmaceutical company would have no incentive to oversell the antibiotic (e.g. EXAMPLE AND REFERENCE).~~ Initiatives to improve the development pipeline for new antibiotics ~~have been proposed and some~~ are being implemented (e.g. the Generating Antibiotics Incentives Now in the U.S. ~~(*17*)~~ and the Innovative Medicines Initiative in Europe ~~(*18*)~~) but cannot be long term solutions because resistance develops quickly to new antibiotics. Initiatives like the Affordable Medicines Facility-malaria, that aimed to conserve the effectiveness of antimalarial drugs, involved a high-level subsidy (aimed at manufacturers, not retailers) and were found to be moderately successful at increasing sales of quality-assured, artemisinin combinations and reducing the use of monotherapies that contribute to drug resistance (*19,20*). Scaling from the size of response relative to GDP in the EU and US (which allocates ~$1bn annually to AMR), we anticipate a global fund of at least $5 billion annually will be needed.

Global architecture

The global response to HIV/AIDS, effective in curtailing that epidemic, was accelerated by the 2001 UNGA on HIV/AIDS (*21*). A clear set of actions tied to targets, financing, institutional commitment to cross-sectoral coordination at the national level, international monitoring and accountability, and civil society participation should also now be reflected in a UNGA plan for AMR. A global architecture must transcend the individual animal and human domains (*22*). Proposed approaches include ones similar to the Intergovernmental Panel on Climate Change, or the Montreal Protocol (*23*).

The current tripartite arrangement between WHO, the Food and Agricultural Organization (FAO), and World Organization for Animal Health (OIE) offers promise but is unlikely to be sustainable given their other priorities. We recommend a new High-level Coordinating Mechanism (HLCM) under the UN Secretary General because: (i) access to effective antimicrobials transcends the remit of WHO, involving animal health and the environment; (ii) non-state actors play an important role; (iii) significant new funding is needed for research and development.

The HLCM consisting of WHO, FAO, OIE, the World Bank, relevant UN agencies and other international organizations, major multisectoral stakeholders and global experts, and reporting to the UN Secretary General should coordinate support for development, implementation and monitoring of national plans and relevant actions. It can raise awareness and financing if the leadership is given seniority within the UN system. A new ~~entity~~ HLCM would allow a more inclusive governing body (e.g. with non-state actor voting rights) as well as substantial engagement with civil society, patient groups, and the private sector.

Financing would likely come through a replenishment process, such as used by the Global Fund and the GAVI Alliance through World Bank Trust Funds (*25*); an organization solicits multi-year donor commitments on a regular schedule (e.g., every three years), rather than every year. Buy-in of countries across the world, particularly G77 members, as well as funders such as the Bill & Melinda Gates Foundation would be essential.

Antibiotic resistance threatens to erase decades of progress in medicine, food security, and public health. Global collective action rooted in national responses is necessary. The UNGA high level meeting on AMR could help shift world opinion, build consensus around core feasible goals, and integrate solutions into policy approaches by UN member states, international organizations, and philanthropies.

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Supplemental Materials
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FIGURE. CAPTION. Based on (8). See SM.

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