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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, 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 ($2 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 be compromising 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 inappropriate given the urgency of the problem. This could avert much of the projected 67% increase in farm animal use between 2010 and 2030 (10). 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, a small fraction of the country’s burden of AMR (10).

Moreover, the costs of improving biogas and biorefinery in farming operations to phase out antimicrobial growth promoters would be largely offset by lowering risk of bioterrorism and costs 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 happen. Globally, this would happen through a multilateral process, as with global movements to phase out, e.g., asbestos or chlorofluorocarbons.

National level restrictions on antibiotic use, efforts 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 targets for reductions in antibiotic consumption is important, it could be accompanied by antimicrobial target antibiotics or actions against the ultimate target of reducing drug-resistant infections. We propose targets in use to reduce levels of a drug resistance index (e.g., the proportion of infections that are resistant), based on weights (11) for the resistance of the eight World Health Organization (WHO) priority pathogens to first line antibiotics, nationally, regionally and globally within 5 years (12).

Reductions should be related to 2010 levels, based on the eight World Health Organization (WHO) priority pathogens to first line antibiotics. We do not specify the scale of reduction – the immediate priority is to prevent increases - but recommend a review (13) as a framework to consider more stringent targets. The temptation given the high drug resistant bacteria chosen, would reflect the unique challenges in low-income and middle-income countries (14).

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...
provide opportunities to strengthen surveil-
lace in countries with poor public health
architecture. Not all surveillance elements
need to be replicated at a national level; in-
tegrating local activities into multi-national
networks may be more efficient, with ap-
propriate structures for data sharing, analy-
sis 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 deve-
opment of new vaccines, diagnostics, novel
therapies and stewardship methods, as well
as traditional antibiotics to ensure availabil-
ity of the "antibiotic umbrella" has been
widely recognized (13). Vaccines, for ani-
mals and humans, face high development
costs and uncertain markets; however, the
GAVI Vaccine Alliance financing mechanism
has been successful in bringing new vac-
cines into wide use.

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

Novel alternatives to traditional antibi-
otics are needed. Multiple non-compound
approaches that target bacteria or the host
have been proposed (14). Antibiotics can in-
teract to synergize, antagonize, or suppress
each other's effects (15), modifying the evo-
lution of resistance.

Financial stimuli for antibiotic develop-
ment must address the lack of incentives for
appropriate use (16) and should enable sus-
tainable access when clinically appropriate. There are proposals for "antibacterial pro-
ecesses," where the pharmaceutical company would have no incentive to develop the antibiotic unless the patient also purchased a vaccine. The U.S. government's "Rapid Antimicrobial Development Program" may provide incentives for antibiotic development.

REFERENCES AND NOTES

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Supplemental Materials

FIGURE: CAPTION: Based on [8] Sect 8.4

Commented [BW2]: We need a brief caption. There likely will not be room for caption text to explain/interpret the data. Instead, it just needs to give the basic info needed to interpret the axes, data source, etc.