Addressing the antibiotic resistance threat

– the role of water, sanitation and hygiene

Antibiotic resistant bacteria are spreading at an alarming rate and some bacterial infections may once again be untreatable. Antibiotic resistance (ABR), conservatively calculated, causes more than 500 000 deaths every year.[1-3] This number is projected to rise dramatically if radical actions are not taken. Lack of effective antibiotics, diagnostics and vaccines threatens the health of millions and hampers fulfilment of several of the Sustainable Development Goals.[4] Access to *effective* antibiotics should be part of every adult and child's right to health.

WHO has drafted a Global Action Plan on Antimicrobial Resistance, adopted by all Member States at the World Health Assembly in 2015.[5] The plan, among other things, calls for Member States to develop National Action Plans. ABR was also discussed at the UN General Assembly in 2016 where Member States recognized the magnitude of this global problem and adopted a Political Declaration to address the issue.

One of the five strategic objectives in the Global Action Plan is to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures. Poor water, sanitation and hygiene (WASH) leads to the spread of infectious diseases, which in turn leads to increased use of antibiotics. To reduce use is critical to limit emergence and spread of antibiotic resistant bacteria.

The burden of resistant bacteria is increasing

- It is estimated that 494 million cases of diarrhoea are treated with antibiotics each year in Brazil, Indonesia, India and Nigeria alone. Universal access to improved water and sanitation in these four countries could cut this number by 60%.[6] Additionally, many cases of diarrhoea should not be treated with antibiotics at all.[7]
- Typhoid fever affects many million people every year. It is caused by *Salmonella* Typhi, and spreads via water and food contaminated with faecal matter. Currently an epidemic of multidrug-resistant *S.* Typhi sweeps across parts of Africa.[8]
- A striking example comes from Blantyre, Malawi, where 782 typhoid cases were identified in 2014, compared to on average 14 per year between 1998 and 2010. Over the same period multidrug-resistant infections increased from 7% to 97%.[9]
- *Campylobacter* is a leading cause of human gastroenteritis globally, and spreads via contaminated food or water. In some cases antibiotic treatment is necessary, but there are increasing levels of resistance to preferred treatments.
- For example, reports from Thailand and Hong Kong describe fluoroquinolone-resistance in more than 80% of clinical *Campylobacter* isolates.[10]

Neonates are particularly affected

- Pooled data from systematic reviews demonstrated that around 40% of sepsis in neonates was due to pathogens resistant to the currently recommended WHO regimens.[11,12]
- Healthcare-associated infections are a major problem around the world. However, neonatal intensive care units have been identified as high-risk settings for transmission of antibiotic resistant pathogens.[13,14]
- As an example, 56% of the neonates in an Ecuadorian hospital were colonized with multidrug-resistant bacteria. The major risk factor for colonization was length of stay at the hospital.[15]
- Many facilities in resource-poor settings lack proper water and sanitation services, which results in low quality of care and lower impact on neonatal mortality and occurrence of healthcare-associated infections in general.[16]

ReAct
Action on Antibiotic Resistance

Access to effective antibiotics should be part of every adult and child's right to health.

The role of the environment in emergence and spread of antibiotic resistance

Currently, drug manufacturing facilities, animal and aquaculture farms, hospitals and municipalities pollute water systems with antibiotic residues and resistant bacteria. Many of the resistance genes today observed in pathogenic bacteria likely originated from environmental bacteria. Antibiotics released into the environment further enrich for resistance genes.

There are at least two distinct threats where this environmental contamination becomes a problem in human health:

1) Facilitation of spread of resistant bacteria
2) Emergence of resistance in bacterial pathogens

- In some regions of the world, >60% of the population carry multidrug-resistant enterobacteria as part of their normal faecal flora. The exact routes of spread are not clear, but environmental contamination likely contributes.[17]

- Antibiotics and resistant bacteria have been detected in surface, ground and drinking water and resistance genes are enriched in river sediments close to wastewater treatment plants.[18,19]

- Extremely high concentrations of antibiotics have been found in waterways nearby antibiotic-manufacturing sites. An Indian wastewater plant that serves ~90 drug manufacturers was found to release 45 kg (99 lbs.) ciprofloxacin into the nearby river every day. As a comparison, daily consumption in Sweden is ~9 kg per day.[20]

- Currently, many intensive animal production systems rely on the use of antibiotics, often at the expense of good hygiene and sanitary conditions. Antibiotic resistant bacteria are frequently identified in farm animals. These bacteria can spread to humans, by direct contact and indirectly via the food chain, water, air and fertilized soils. The exact magnitude of the problem is not known, but evidence of animal-to-human spread of resistant bacteria continues to increase.[21]

- New antibiotic resistance mechanisms can develop in animals. A recent and serious example is the emergence of bacteria with transferable colistin-resistance. Colistin is a drug of last resort to treat serious resistant infections in humans. However, colistin is also used widely in livestock. Numerous lines of evidence indicate that this type of colistin-resistance originated in animals and then spread to humans.[22,23]

How improved WASH can limit antibiotic resistance

- By reducing the need for antibiotics through reducing the incidence of infection. Hygiene and infection prevention is the first line of defence against the use of antibiotics and thereby ABR. One important focus area is to prevent infections at the time of birth for both newborns and mothers.

- By breaking the chain of transmission of resistant bacteria between people, animals, food, water and the environment. Efforts to e.g. end open defecation and provide improved sanitation facilities are important interventions to limit spread of resistant bacteria.

- By reducing release of antibiotics and resistant bacteria into the environment.

Options for action

Policy

• The Global Action Plan on Antimicrobial Resistance urges countries to develop National Action Plans. These are intended to cover multiple perspectives of healthcare and beyond. UN organisations and other key stakeholders with a strong national presence are uniquely positioned to facilitate the intersectorial collaboration and provide the expert advice needed to ensure implementation of actions on ABR.

• Efforts to improve WASH have direct positive effects on limiting ABR development and spread, and on quality of care. A key strategy is to mainstream ABR into on-going efforts and existing strategies such as the global action plan on WASH in healthcare facilities[16], global handwashing campaigns[24] and sanitation initiatives[25].

Research and generation of evidence

• Provide technical advice and support for implementation of WASH interventions in relation to ABR. This could include waste management improvement or hand hygiene campaigns (that address e.g. water point access, hand washing facilities in the delivery room, procurement of soap and local production of alcohol-based hand rub in health facilities[26]).

• Perform systematic investigations of the impact of different WASH interventions on specific healthcare-associated infections, including those caused by resistant bacteria.

Advocacy and education

• Advocate for increased investments in WASH infrastructure in low and middle income countries. ABR provides an additional entry point at country level to advocate for joint action between e.g. ministries responsible for health and for water and sanitation.

• Advocate for regulation of release of antibiotics from manufacturing facilities and for improved handling of waste from sewage treatment plants.[27]

• Develop messages for effective communication for behavioural change. Organize awareness-raising activities on ABR to empower community and civil society.

Collaboration across UN organisations around existing plans such as the Global Strategy for Women's, Children's and Adolescent's Health 2016-2030 is key. Organisations such as WaterAid already advocate for the importance of WASH to limit ABR, but other global CSOs and major funders also need to be brought on board.

TOOLBOX

The ReAct Toolbox is a web-based knowledge repository for antibiotic resistance that collects:

- Scientifically accurate information
- Practical advice
- Links to useful resources
- Examples from the field

Access the Toolbox:

www.reactgroup.org/toolbox

Photographs: Photoshare

References

1. *Phumart, P. et al. Health and Economic Impacts of Antimicrobial Resistant Infections in Thailand: A Preliminary Study. J. Health Sys. Res. 6, 352–360 (2012).**
2. *Centers for Disease Control and Prevention - CDC. Antibiotic resistance threats in the United States. (2013).**
3. *European Centre for Disease Prevention and Control - ECDC, European Medicines Agency - EMA. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and development of new antibacterial agents Luxembourg: EUR-OP. (2009).**

   **Data in references 1-3 was used to extrapolate the worldwide burden of ABR (conservative estimate)*

4. *Jasovsky, D. et al. Antimicrobial Resistance - A Threat to the World's Sustainable Development. Dag Hammarskjöld Foundation Dev. Dialogue Pap. 16, (2016).*
5. *World Health Organization. Global Action Plan on Antimicrobial Resistance. < http://www.who.int/drugresistance/global_action_plan/en/> (2015).*
6. *The Review on Antimicrobial Resistance. Infection Prevention, Control and Surveillance: Limiting the Development and Spread of Drug Resistance. (2016).*
7. *UNICEF. Pneumonia and diarrhoea: Tackling the deadliest diseases for the world's poorest children. (2012).*
8. *Wong, V. K. et al. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. Nat. Genet. 47, 632-639 (2015).*
9. *Feasey, N. A. et al. Rapid Emergence of Multidrug Resistant, H58-Lineage Salmonella Typhi in Blantyre, Malawi. PLoS Negl. Trop. Dis. 9, e0003748 (2015).*
10. *Luangtongkum, T. Antibiotic resistance in Campylobacter: emergence, transmission and persistence. Future Microbiol. 4,189-200 (2009).*
11. *Downie, L. et al. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics - systematic review and meta-analysis. Arch. Dis. Child. 98, 146–54 (2013).*
12. *Le Doare, K. et al. Systematic Review of Antibiotic Resistance Rates Among Gram-Negative Bacteria in Children With Sepsis in Resource-Limited Countries. J. Pediatric Infect. Dis. Soc. 4, 11–20 (2015).*
13. *Russell, A. B. et al. Improving antibiotic prescribing in neonatal units: time to act. Arch. Dis. Child. Fetal Neonatal Ed. 97, F141–146 (2012).*
14. *Zaidi, A. K. et al. Hospital-acquired neonatal infections in developing countries. Lancet. 365, 1175-1188 (2005).*
15. *Nordberg, V. et al. High Proportion of Intestinal Colonization with Successful Epidemic Clones of ESBL-Producing Enterobacteriaceae in a Neonatal Intensive Care Unit in Ecuador. PLoS One. 11, e76597 (2013).*
16. *WHO/UNICEF/SHARE Workshop Report: Water, sanitation and hygiene in health care facilities - Global strategy, burden of disease, and evidence and action priorities. (2016).*
17. *Woerther, P. L. et al. Trends in Human Fecal Carriage of Extended-Spectrum beta-Lactamases in the Community: Toward the Globalization of CTX-M. Clin. Microbiol. Rev. 26, 744-758 (2013).*
18. *Finley, R. L. et al. The Scourge of Antibiotic Resistance: The Important Role of the Environment. Clin. Infect. Dis. 57, 704-710 (2013).*
19. *Kristiansson, E. et al. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. PLoS One 6, e17038 (2011).*
20. *Larsson, D. G. J. et al. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J. Hazard. Mater. 148, 751-755 (2007).*
21. *Marshall, B. M. et al. Food Animals and Antimicrobials: Impacts on Human Health. Clin. Microbiol. Rev. 24, 718-733 (2011).*
22. *European Medicines Agency. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. (2016).*
23. *Liu, Y. Y. et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect. Dis. 16, 161-168 (2016).*
24. *World Health Organization. SAVE LIVES: Clean Your Hands. < http://www.who.int/gpsc/5may/en/>, accessed June 30 (2016).*
25. *Sustainable sanitation alliance. <http://www.susana.org/en/>, accessed June 30 (2016).*
26. *World Health Organization. Policy brief: draft for consultation (version 0) - How to expand access to affordable hand hygiene products to prevent health care-associated infection and reduce the spread of antimicrobial resistance. (2016).*
27. *The Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: final report and recommendations. (2016).*