Antibiotic use, resistance and the link to nutrition

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 of the Global Action Plan is to reduce the misuse and overuse of antibiotics in all sectors, to slow development of resistance as much as possible. In addition to the contribution to resistance, misuse of antibiotics is also costly. Estimates have shown that the suboptimal use of antibiotics costs $55 billion/year, which equals approximately 0.9% of global total health expenditure.[6]

The relevance for those working in nutrition are for example the current WHO guidelines that recommend giving routine antibiotics for children with severe acute malnutrition (SAM), the risk of transfer of resistant bacteria and resistance genes from food and the potential to reduce unnecessary use of antibiotics by interventions that decrease the incidence of infections.

The link between health, nutritional status and water, sanitation and hygiene (WASH)

- Reducing the incidence of infections and preventing malnutrition by e.g. encouraging breastfeeding and improving water and sanitation standards is key for reducing antibiotic use.

- 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%.[7] Additionally, many cases of diarrhoea should not be treated with antibiotics at all.[8] Early clinical interventions introducing Oral Rehydration Salts coupled with zinc supplementation have the potential to reduce unnecessary use of antibiotics as well.[9]

Antibiotic resistance and the link to food

- Research has demonstrated that proximity to industrial swine operations and crop fields where swine manure is applied as fertilizer is a risk factor for developing antibiotic-resistant infections.[17] In addition, numerous studies have demonstrated similarity among bacteria from urinary tract infections in humans and bacteria from retail chicken samples,[18-20] suggesting food as the primary pathway of transmission.

- For example, 75% of bacteria on chicken meat in Kenya were resistant to at least one antibiotic.[21] These bacteria can spread to humans, by direct contact and indirectly via the food chain, water, air and manure and sludge-fertilized soils.

- At present we do not have complete knowledge on the magnitude of transmission between food animals and humans, but we know that it does occur and there is an ever-expanding volume of evidence reporting animal-to-human spread of resistant bacteria.[22]

- In addition, new antibiotic resistance mechanisms can emerge from the animal sector. A recent and serious example on this is the emergence of mobile resistance to colistin, an antibiotic of last resort. Findings indicate a flow from animals to humans.[23]

The role of antibiotic exposure on the gut flora

- Current studies report loss of biodiversity in the normal gut flora after antibiotic exposure, suggesting that some people's microbiomes may take longer to recover than others.[10] The recovery period represents a vulnerable time, since not all members of the microbial community are present to suppress potential pathogens and hence prevent infection.[11]

- Mode of delivery, breastfeeding and antibiotic use have also been shown to impact the composition of the gut microbiome flora and to have subsequent impact on diarrhoea morbidity and mortality.[12-15]

- Prolonged antibiotic use decreases microbial diversity and promotes a microbiota that is associated with neonatal sepsis.[16]

- More than 60% of the population in some areas carry multi-drug resistant bacteria in their normal flora.[32]

Conflicting evidence on guidelines on antibiotic use for Severe Acute Malnutrition (SAM)

- A review in 2013 showed that the underlying evidence to continue with routine amoxicillin therapy in children with uncomplicated SAM is weak, especially for populations with low HIV prevalence.[24]

- In contrast, a later study in Malawi showed that both amoxicillin and cefdinir significantly reduced the risk of treatment failure and death as compared with placebo.[25] However the study was of a high-risk population, characterized by a relatively high burden of kwashiorkor and HIV infection.

- However, a more recent study published in 2016 by MSF found no difference in nutritional recovery between children receiving amoxicillin and placebo.[26] The study enrolled 2400 children with uncomplicated SAM in Niger. The study population had low HIV-prevalence and malnutrition was predominantly due to marasmus.

- The MSF study still demonstrated some advantages with amoxicillin over placebo (such as decreased risk of transfer to hospital for acute gastroenteritis). However among hospitalized children, there were no significant differences in the mean length of stay. This could suggest that adequate inpatient care could be sufficient to mitigate the risk of hospitalisation associated with the absence of routine antibiotic use.

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

Antibiotic use for SAM represents a large fraction of total use in certain countries

- Routine use of antibiotics for the treatment of SAM accounted for 15% of all antibiotic use among children younger than 5 years of age in the district studied in Niger.[26]

- As this represents a large fraction of total use and there is conflicting evidence of which populations benefit from this therapy, further research is urgently needed.

Other antibiotics also considered for mass administration to improve nutritional status

- Azithromycin is used for mass treatment of trachoma[27], and has also been linked to reduced morbidity and mortality in children.[28,29]

- However several trials have shown that mass administration of azithromycin does not lead to improved nutritional status in children and that any mortality benefits probably has other causes.[30,31]

- As azithromycin is also used to treat for example drug resistant *Shigella, Campylobacter,* gonhorrea and typhoid fever, resistance development would have vast consequences.

In summary, any large-scale use of antibiotics needs to be weighed against individual benefits and consequences of unnecessary antibiotic use, including costs.

In addition, the possibility of serious long-term harm both to individuals and to global populations if resistance rates would increase should be considered. If the benefit of the mass treatment is greater for the individual, efforts should be made to track resistance development to the antibiotics used.

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 health care 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 fight malnutrition and improve food security have direct positive effects on limiting ABR development and spread, and on quality of care. To maintain antibiotic effectiveness, capitalizing on existing strategies and including indicators to enable transparent monitoring and evaluation is key.

Advocacy and education

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

• Include education also on the risks of ABR when addressing the importance of the right cooking temperature for meat, washing/cooking vegetables etc.

Research and generation of evidence

• How many children receive antibiotics for SAM and what are the characteristics of these children? Which antibiotics are given and for which duration?

• Which subpopulations of children would actually benefit from antibiotic treatment for SAM. Which would not benefit? What antibiotics give the best effect combined with the lowest risk for resistance development?

• Are resistance rates higher in populations that have received antibiotics for SAM, or through mass administration? Are there long-term changes in their microbiota?

• Is there increased risk of carriage or infection with resistant bacteria as a consequence of living in close proximity to livestock in low-resource settings?

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. To expand our knowledge, universities, CSOs and major funders also need to be brought on board.

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. (2015). at < http://www.who.int/drugresistance/global_action_plan/en/>*
6. *Dutch Ministry of Health, Welfare and Sport. Invitational Ministerial Summit: The benefits of responsible use of medicines. Setting policies for better and cost effective healthcare. (2012).*
7. *The Review on Antimicrobial Resistance. Infection Prevention, Control and Surveillance: Limiting the Development and Spread of Drug Resistance. (2016).*
8. *UNICEF. Pneumonia and diarrhoea: Tackling the deadliest diseases for the world's poorest children. (2012).*
9. *Zwisler, G. et al. Treatment of diarrhea in young children: results from surveys on the perception and use of oral rehydration solutions, antibiotics, and other therapies in India and Kenya. J. Glob. Health 3, 010403 (2013).*
10. *Francino, M. P. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. Frontiers in Microbiology. 6:1543 (2015).*
11. *Vangay, P. et al. Antibiotics, Pediatric Dysbiosis, and Disease, Cell Host Microbe 17, 553–64 (2015).*
12. *Madan, J. C. et al. Association of Cesarean Delivery and Formula Supplementation With the Intestinal Microbiome of 6-Week-Old Infants. JAMA Pediatr.170, 212-219 (2016).*
13. *Bokulich, N. A. et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci. Transl. Med. 8, 343ra82 (2016).*
14. *Faber, F. et al. Host-mediated sugar oxidation promotes post-antibiotic pathogen expansion. Nature 534, 697–699 (2016).*
15. *Lamberti, L. M. et al. Breastfeeding and the risk for diarrhea morbidity and mortality. BMC Public Health 11, S15 (2011).*
16. *Madan, J. C. et al. Gut Microbial Colonisation in Premature Neonates Predicts Neonatal Sepsis. Archives of disease in child hood. Fetal and neonatal edition. 97, F456-62 (2012).*
17. *Casey, J. A. et al. High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant Staphylococcus aureus infection in Pennsylvania. JAMA Intern. Med. 173, 1980–90 (2013).*
18. *Davis, G. S. et al. Intermingled Klebsiella pneumoniae Populations Between Retail Meats and Human Urinary Tract Infections. Clin. Infect. Dis. 61, 892–9 (2015).*
19. *Leverstein-van Hall, M. A. et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin. Microbiol. Infect. 17, 873–80 (2011).*
20. *Vincent, C. et al. Food reservoir for Escherichia coli causing urinary tract infections. Emerg. Infect. Dis. 16, 88–95 (2010).*
21. *Odwar, J. A. et al. A cross-sectional study on the microbiological quality and safety of raw chicken meats sold in Nairobi, Kenya. BMC Res Notes. 7:627 (2014).*
22. *Marshall, B. M. and Levy, SB. Food Animals and Antimicrobials: Impacts on Human Health Clin. Microbiol. 24, 718-733 (2011).*
23. *European Medicines Agency. Updated advice on the use of colistin products in animals within the European Union: develop ment of resistance and possible impact on human and animal health. (2016). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500207233.pdf>*
24. *Alcoba, G. et al. Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and meta-analysis. PLoS One 8, e53184 (2013).*
25. *Trehan, I. et al. Antibiotics as part of the management of severe acute malnutrition. N. Engl. J. Med. 368, 425–35 (2013).*
26. *Isanaka, S. et al. Routine Amoxicillin for Uncomplicated Severe Acute Malnutrition in Children. N. Engl. J. Med. 374, 444–53 (2016).*
27. *Solomon, A. W. et al. Trachoma control: a guide for programme managers. World Health Organization, London School of Hygiene & Tropical Medicine, International Trachoma Initiative. (2006).*
28. *See, C. W. et al. The Effect of Mass Azithromycin Distribution on Childhood Mortality: Beliefs and Estimates of Efficacy. Am. J. Trop. Med. Hyg. 93, 1106–9 (2015).*
29. *Kigen, G. et al. Collateral benefits arising from mass administration of azithromycin in the control of active trachoma in resource limited settings. Pan Afr. Med. J. 19, 256 (2014).*
30. *Amza, A. et al. Does mass azithromycin distribution impact child growth and nutrition in Niger? A cluster-randomized trial. PLoS Negl. Trop. Dis. 8, e3128 (2014).*
31. *Burr, S. E. et al. Anthropometric indices of Gambian children after one or three annual rounds of mass drug administration with azithromycin for trachoma control. BMC Public Health 14, 1176 (2014).*
32. *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).*