Antibiotic resistance

– undoing progress in maternal and child health

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.

The importance of effective antibiotics for child health

Maternal and child deaths have halved worldwide over the past two decades. Reduction of pneumonia, diarrhoea, and measles accounted for half of this number. However, neonatal sepsis showed one of the slowest rates of improvement.[6] ABR and the lack of access to effective antibiotics threaten to undo the gains made and hamper further improvements.

Both lack of access to effective antibiotics and resistance contribute to the disease burden

- Targeted access to antibiotics could avert approximately 445 000 community-acquired pneumonia deaths in children aged younger than 5 years.[7]
- Globally, it is estimated that 214 000 neonatal sepsis deaths annually - more than a third of the total number of deaths - are attributable to resistant pathogens.[7]
- Use of antibiotics contributes to carriage of resistant bacteria, which can persist for several months after treatment. It also increases the risk for subsequent infection with resistant bacteria.[8-10]

To reduce unnecessary use of antibiotics, prevention is key

- 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%.[11] Additionally, many cases of diarrhoea should not be treated with antibiotics at all.[12]
- 11.4 million antibiotic days could be avoided annually as a result of universal pneumococcal conjugate vaccine availability.[7]

Resistance rates are not only high in hospitals – studies in the community in India showed resistance rates of up to 70% already more than 10 years ago.[13] More recent studies of community-acquired neonatal and infant sepsis show high rates of resistance in low-income countries.[14] In addition, more than 60% of the population in some areas carry multi-drug resistant bacteria in their normal flora.[28]

ABR also has a significant impact on cost of treatments. It is estimated that the median overall cost to treat a resistant bacterial infection is around 700 USD, corresponding to more than a year's wages of a rural worker in India.[15] Novel treatments for multi drug-resistant infections can cost up to tens of thousands of US dollars, which ultimately make the medicines unaffordable for many.[16]

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

Sepsis

- Further progress in decreasing child mortality depends on reducing the 2.9 million neonatal deaths each year, of which 23% are directly due to infection.[17]
- Neonatal intensive care units have been identified as high-risk areas for transmission of antibiotic resistant pathogens.[18,19]
- Pooled data from systematic reviews demonstrate that around 40% of sepsis in neonates was due to pathogens that were resistant to the currently recommended WHO regimens.[14,20]
- In some facilities in the AFRO region, 100% of *Klebsiella pneumoniae* isolates were resistant to ampicillin. In the SEARO region, up to 83% of *E. coli* isolates were gentamicin-resistant. [20]

Current actions to reduce global neonatal mortality focus mainly on improving quality of care at birth and assistance to mothers during labour. Quality of care should include minimising neonatal infections as well as addressing the threat of ineffective antibiotics due to ABR. Limited surveillance data hamper accurate assessments of guidelines and the actual rates of ABR in children.[21] Further research is needed, as the optimum choice of drug, dose, and duration to treat neonatal sepsis is unknown in settings with high resistance to WHO first-line empirical therapy.

Pneumonia

- Pneumonia deaths declined by 51% during the MDG era, but still killed 922 000 children in 2015 and accounted for 16% of all deaths in children under 5.[22]
- The need to adapt guidelines to the changing resistance situation is great. Though warnings of resistance to co-trimoxazole in *Streptococcus pneumoniae* came early, it took many years for the recommendations to change (to amoxicillin) and even longer to implement the recommendations.[23,24, 29]
- A Gambian vaccination programme reduced the incidence of invasive pneumococcal disease in children aged 2-59 months by 55%.[25]
- High prices are a barrier for access to pneumonia vaccine, making it unavailable for an increasing number of low- and middle-income countries.
- Rapid diagnostic tests for malaria enabled better diagnostic outcomes but also contributed to an increased use of antibiotics.[26] This points to the need for better diagnostics also for bacterial diseases, as well as integrated programs with alternative appropriate treatment.

The focus of actions taken will be highly different depending on context – in some countries or regions, the emphasis will be on expanding access and in some, reducing excess. Regardless, systems for *sustainable* access to *effective* antibiotics are needed.

Additionally, attention should be given to updating current clinical practices for children. A revised version of the IMCI, the ALMANACH algorithm, reduced antibiotic prescription by 80% while improving clinical outcome.[27]

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.

• Interventions improving maternal and child health have direct positive effect 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, such as % of population with access to effective antibiotics, is key.

Research and generation of evidence

• Contribute to global surveillance programmes collecting ABR data as they are critical to allow benchmarking and design properly targeted interventions. Support monitoring of emerging resistance.

• Evaluate interventions aimed at decreasing inappropriate use of antibiotics.

Advocacy and education

• Advocate for development of affordable quality antibiotics, vaccines and diagnostics.

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

• Provide informal education of caretakers of children (parents, community health workers).

• Support development of evidence-based antibiotic guidelines and monitor adherence to guidelines and recommendations from international organisations, such as WHO.

Regulatory and supply chain management

• Enhance equitable access to quality antibiotics simultaneously with conservation efforts (this includes involving and working with the private sector, from pharmaceutical companies to local private practices or pharmacies).

• Support supply chain strengthening to avoid stock-outs and poor management of stocks.

• Support quality assurance programmes of medicines including antibiotics.

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. Global CSOs and major funders also need to be brought on board. Collaborative platforms such as the Inter-agency Supply Chain Group could support efforts in assuring antibiotic quality. Faith-based organisations, such as the Ecumenical Pharmaceutical Network provide a large fraction of healthcare in some countries.

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). < http://www.who.int/drugresistance/global_action_plan/en/>*
6. *Liu, L. et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 385, 430–440 (2014).*
7. *Laxminarayan, R. et al. Access to effective antimicrobials: a worldwide challenge. Lancet 387, 168–175 (2016).*
8. *Bryce, A. et al. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ 352, i939 (2016).*
9. *Karanika, S. et al. Colonization With Methicillin-resistant Staphylococcus aureus and Risk for Infection Among Asymptomatic Athletes: A Systematic Review and Metaanalysis. Clin. Infect. Dis. ciw240 (2016).*
10. *Rodríguez-Baño, J. et al. Risk-factors for emerging bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Clin. Microbiol. Infect. 14, 180–183 (2008).*
11. *The Review on Antimicrobial Resistance. Infection Prevention, Control and Surveillance: Limiting the Development and Spread of Drug Resistance. (2016).*
12. *UNICEF. Pneumonia and diarrhoea: Tackling the deadliest diseases for the world's poorest children. (2012).*
13. *Holloway, K. et al. Community-based surveillance of antimicrobial use and resistance in resource-constrained settings: report on five pilot projects. Geneva: WHO (2009).*
14. *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).*
15. *Chandy, S. J. et al. High cost burden and health consequences of antibiotic resistance: the price to pay. J. Infect. Dev. Ctries. 8, 1096–102 (2014).*
16. *Cecchini, M. et al. Antimicrobial Resistance in G7 Countries and Beyond: Economic Issues, Policies and Options for Action. (2015).*
17. *Lawn, J. E. et al. Every Newborn: progress, priorities, and potential beyond survival. Lancet 384, 189–205 (2014).*
18. *Russell, A. B. et al. Improving antibiotic prescribing in neonatal units: time to act. Arch. Dis. Child. Fetal Neonatal Ed. 97, F141–6 (2012).*
19. *Zaidi, A. K. et al. Hospital-acquired neonatal infections in developing countries. Lancet. 365, 1175-1188 (2005).*
20. *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).*
21. *World Health Organization. Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources. (2005).*
22. *UNICEF. Global Databases: Pneumonia - Multiple Indicator Cluster Surveys (MICS), Demographic and Health Surveys (DHS) and other national surveys. (2015).*
23. *Okeke, R. et al. Antimicrobial Resistance in Developing Countries. Part I: Recent Trends and Current Status. Lancet Infect. Dis. 5, 481-493 (2005).*
24. *Feikin, D. R. et al. Increased Carriage of Trimethoprim/Sulfamethoxazole- Resistant Streptococcus Pneumoniae in Malawian Children after Treatment for Malaria with Sulfadoxine/Pyrimethamine. J. Infect. Dis. 181, 1501-1505 (2000).*
25. *Mackenzie, G. A. et al. Effect of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease in The Gambia: a population-based surveillance study. Lancet. Infect. Dis. 16, 703-711 (2016).*
26. *D'Acremont, V. et al. Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. Malar J. 10:107 (2011).*
27. *Shao, A. F. et al. New Algorithm for Managing Childhood Illness Using Mobile Technology (ALMANACH): A Controlled Non-Inferiority Study on Clinical Outcome and Antibiotic Use in Tanzania. PLoS One 10, e0132316 (2015).*
28. *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).*
29. *Daulare et al. Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance. J Law Med Ethics. Summer;43, Suppl 3:17-21 (2015).*

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