



Opinion paper

Antimicrobial resistance is a global problem – a UK perspective

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ABSTRACT

Increasingly we are reaching a situation where current antimicrobial medicines are no longer effective for common infections, and antimicrobial resistance (AMR) is now a global public health crisis. The reliance on antimicrobials such as antibiotics has become a major issue for both medicine and agriculture, particularly given the slow development of new medicines and pharmaceutical industry investment. The UK government has been working with other international bodies in the search for solutions to the many challenges AMR poses. Herbal medicines may provide a useful modality in the fight against AMR and can work solely or in tandem with current antimicrobial approaches. Recommendations for herbal medicine use during the COVID-19 viral pandemic have featured in Chinese national guidelines and policies, but UK strategies have no such guidance on herbal treatment for any infectious disease. More research is urgently needed to explore the biological plausibility and safety of herbal medicines to manage AMR. AMR is universal, affecting anyone and everyone, at any age and in any country. Investigating how such approaches can be integrated into western medicine will be important to elucidate.

1. Anti-microbial resistance (AMR), an evolving global threat

At the start of the 20th century, major advancements in antimicrobial drug discovery and infection control helped turn the tide in human life expectancy. In the field of bacterial infection, this was facilitated by the discovery of penicillin in 1928 by Sir Alexander Fleming [1]. Unfortunately, as antibiotics became more widely used, bacteria responded by developing various forms of resistance to these treatments, which has rapidly accelerated creating a serious and global problem [2]. Very few antimicrobials have been developed in the last two decades which is now limiting the scope of action [3]. Currently, antibiotics also lack diversity in their cellular targets and new antibiotic classes are urgently needed as treatment choices become limited [3]. As the use of these antibiotics has increased so has the level of response, and complexity of resistance by microbes [4].

Globally, resistance in *Klebsiella pneumoniae* to the last resort treatment (carbapenem antibiotics) has spread to all areas of the world [5]. In some countries, because of resistance, carbapenem antibiotics do not work in more than half of people treated for *K. pneumoniae* infections [6].

Resistance in *E. coli* is extensive. Fluoroquinolone antibiotics are one of the most widely used medicines for the treatment of urinary tract infections. Treatment is now ineffective in more than 50% of patients in many parts of the world [7]. Treatment failure to third-generation cephalosporin antibiotics (the last resort of medicine) for gonorrhoea has been confirmed in at least 10 countries (Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden and the United Kingdom of Great Britain and Northern Ireland) [5]. *Staphylococcus aureus* resistance is widespread. People infected with MRSA (methicillin-resistant *Staphylococcus aureus*) are estimated to be 64% more likely to die than people with a non-resistant form of the infection. Colistin is the last resort treatment for life-threatening infections caused by Enterobacteriaceae, which are resistant to carbapenems. Resistance to Colistin has recently been detected in several countries and regions, making infections caused by such bacteria untreatable [8].

The O' Neill report on behalf of the UK government predicted that by 2050, AMR will claim 10 million lives a year, and will overtake the number of people dying from cancer (8.2 million each year) [9]. From 2000 to 2010 the rapidly emerging economies of the BRICS (Brazil, Russia, India, China, and South Africa) countries contributed to 76% of

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the growth in antibiotic consumption. Data suggests that the top three consumers are India at 12.9 billion units, China at 10.0 billion units, and USA at 6.8 billion units in 2010 [9]. In BRICS countries, the increase in antibiotic misuse has been partly due to the increasing size of the population, but also improved drug access and socioeconomic status. The absence of antibiotic policies has also played an important role. However, the USA has the highest level of antibiotic misuse for both humans and livestock and is also where antimicrobial stewardship programmes are not widely implemented [10].

This scenario is further compounded by the lack of discovery and development of new antimicrobial medicines coming into the market.

2. An International Priority

AMR has become a priority for all governments and agencies [9,11–12] particularly in response to the 2015 WHO ‘Global Action Plan on Antimicrobial Resistance’, in which Dr. Chan, the former Director-General, stated unequivocally that:

“Antimicrobial resistance threatens the very core of modern medicine and the sustainability of an effective, global public health response to the enduring threat from infectious diseases.”

The overall goal of this Action Plan was to ensure a continuing ability to treat and prevent infectious diseases with effective and safe medicines but the Plan also insisted that this must also be “*accessible to all who need them*”. The Plan’s second objective was to “*strengthen the knowledge and evidence base through surveillance and research*”, further qualifying that this research should address important gaps in knowledge for the treatment of bacterial infections “*especially in low resource settings.*”

The 2015 AMR report further identified that many common medical conditions (identifying tuberculosis, but also HIV/AIDS, malaria, sexually transmitted diseases, urinary tract infections, pneumonia, blood-stream infections, and food poisoning) had become resistant to a wide range of antimicrobial medicines, forcing the use of ‘last-resort’ medicines that are costly, hazardous and often unavailable or unaffordable in low and middle-income countries.

As the World Health Organisation (WHO), has stated anti-microbial resistance (AMR) has become one of the biggest threats to global health, development, and food security [13]. It has given rise to a situation where microbes no longer respond to current usual treatment such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics. Given that antimicrobial medicines are an integral part of modern healthcare, and resistance has the potential to undermine modern healthcare systems; antimicrobials are lifesaving and underpin a wide variety of medical treatments such as cancer treatments, surgery, and organ transplantation [14].

Production of new, stronger antimicrobials should be of high importance, however, there are limited incentives for drug companies to develop new ones [15]. Due to the unfavourable regulatory climate, multiple company mergers and the low financial returns associated with antibiotic drug development have led to the withdrawal of many pharmaceutical companies from the field. Natural product research may hold some promise in providing new molecules as a basis for discovery [16].

3. Anti-microbial resistance and the UK

In the words of Professor Dame Sally Davies, the former Chief Medical Officer in England: “Antimicrobial resistance poses a catastrophic threat” [17]. As mentioned above AMR has become a priority for the UK government and in 2014 it commissioned a review of the current situation with recommendations for the future. Further research by Public Health England in September 2019, outlining its disease strategy for 2020–2025 included goals to make the UK a world player in tackling AMR which included developing the infection prevention

workforce, working on innovative diagnostic technologies and reducing the risks posed by resistant bacteria [18].

In the UK, around half of the antibiotics by weight consumed (491 tonnes) are for human use, and 80% of these are prescribed in primary care. These medicines are mainly (about 60%) used in acute respiratory tract infections (ARTIs) [19]. Although research evidence has suggested that antibiotics offer little benefit for self-limiting conditions such as coughs, colds and viral sore throats, a recent survey suggested half of patients presenting with these concerns were prescribed an antibiotic [20].

4. Agricultural and environmental use of antibiotics

The transmission of AMR is caused by a combination of misuse of antimicrobials does not only occur in humans but also in animals, agricultural practices, and the environment, including the control of post-antibiotic use in soils and waterways [21].

In the UK, 50% of antibiotics are used in agricultural practice and this use is predicted to increase by 67% from 2010 to 2030 [22]. Animal husbandry in the USA accounts for 70% of the consumption of medically important antimicrobials, more than double that of human consumption [23].

The United Kingdom Research and Innovation (UKRI) in the UK and the Department of Biotechnology (DBT), Ministry of Science & Technology, Government of India are working in partnership to fund research programmes with a focus on tackling AMR in the environment from antimicrobial manufacturing waste [24].

5. International governmental collaboration on AMR

Working alone is not an option and the UK has funded international partnerships to seek global solutions to tackle AMR. By collaborating there are opportunities for developing new antimicrobials to control infection. This will not be possible unless there are also public health initiatives that focus on prevention and appropriate prescribing to reduce health-associated infections [9]. This means wider engagement with the wider communities, clinicians, vets, farmers, and by managing patient expectations to reduce threats of AMR WHO [12,13,20]. Global pandemics are expected given the increasing movement of people across continents, health inequalities, a growing elderly population, AMR in the food chain, and climate change, all provide the medium which will lead to the development of new viruses [12].

In October 2018, the UK’s Department of Health announced awards of up to £32million of capital funding for research into AMR. Various international partnerships have been funded by the UK, most recently £5 million was given to 5 research partnerships between the UK and Argentina to focus on the use of antimicrobials in livestock production, a primary contributor to the spread and development of AMR. Drug-resistant microbes transmitted for animals to humans pose a significant threat [22]. Other research funding (The Fleming Fund) has been provided to strengthen existing surveillance systems tracking AMR in Africa and Asia.

In July 2019, the National Institute for Health and Care Excellence (NICE) and NHS England and NHS Improvement launched the testing of a ‘subscription’ style model to pay pharmaceutical companies upfront for access to drugs based on their usefulness to the National Health Service (NHS). Currently, drug companies are paid for the volume of antibiotics sold while the NHS is trying to reduce their use and prevent AMR. The ‘**Keep antibiotics Working Campaign**’ was launched again in November 2019 during the ‘coughs and cold season’ to help reduce inappropriate use of antibiotics.

6. Strategies to minimise the use of antibiotics

Limiting the unnecessary use of antibiotics, improvements in hand-hygiene compliance, in the form of educational programmes, and better

access to clean water and effective sanitation would prevent the spread of infection. Researchers at the University of Southampton, UK have been testing strategies to limit antibiotic use. These have included better prevention by using digital intervention to promote hand-washing [25], better prediction and targeting infection by developing clinical scores and near-patient tests [26,27], and have pioneered the use of the delayed or 'just in case prescription' [28].

The Political Declaration signed at the end of the G20 Summit in Argentina in October 2018 included a significant paragraph (Paragraph 15) which encouraged the WHO and the international community to develop an action plan through multi-sectoral collaboration to meet the health-related aspects of the Sustainable Development Goals by 2030. It specifically mentioned the threat of AMR as follows G20 [29]:

"We recognize the need for further multi-sectoral action to reduce the spread of AMR, as it is increasingly becoming a global responsibility."

Whilst not specifically linking the successful treatment of AMR to Universal Health Coverage (UHC) it was still implied, and then linked UHC to Traditional and Complementary medicine (T&CM):

"We re-affirm the need for stronger health systems providing cost effective and evidence-based intervention to achieve better access to health care and to improve its quality and affordability to move towards Universal Health Coverage (UHC), in line with their national contexts and priorities. This may encompass, where appropriate, scientifically proven traditional and complementary medicine, assuring the safety, quality, and effectiveness of health services."

The challenges of providing effective health care in many countries could include traditional and complementary medicine - particularly if it is safe, appropriate, affordable, and evidence-based – and as such they endorsed fresh efforts to investigate (and 'scientifically prove') Traditional and Complementary Medicine.

7. Herbal medicines, alternatives to antibiotics

In the search for new antibiotics, research into herbal medicines may prove to be fruitful. Herbal medicines have been used for centuries to treat infectious conditions [30]. They are readily available for patients to buy themselves and appear to be increasingly popular particularly in the UK. This growing public interest in herbs could reduce reliance on antibiotics, especially for self-limiting infections. A recent WHO report on traditional medicines noted that the majority of the world's population depends on traditional medicines for primary healthcare including the treatment of infections [31]. Plant secondary metabolites have already demonstrated their potential as antimicrobials when used alone and or synergistically, or as potentiators of other antimicrobial medicines. The use of these metabolites and herbal medicines as resistance-modifying agents (RMAs) represents an increasingly active research area. Phytomedicines frequently act through different mechanisms than conventional antibiotics and could, therefore be of use in the treatment of resistant bacteria. Plant extracts have great potential as antimicrobial compounds against microorganisms especially in addressing the therapeutic vacuum in managing symptoms or acting as antimicrobial medicines themselves. The therapeutic utility of these products, will, however, require further research and undergo strict quality control to guarantee product consistency [32].

8. Herbal medicine projects in the UK

Researchers at the University of Southampton are currently working to find safe and effective alternatives to antibiotics with a strong emphasis on the use of herbal medicines for both respiratory and urinary tract infections. Recent and ongoing trials on herbal medicine include investigating: *Pelargonium sidoides* for lower respiratory tract infections

(HATRIC); *Andrographis paniculata* for respiratory tract infections (GRAPHALO); NSAIDs and a herbal product (*Arctostaphylos Uva ursi*) for urinary tract infection (ATAFUTI), and Chinese herbal medicine for recurrent urinary tract infections (RUTI) [33].

To support the development and clinical evaluation of new products and services, the UK Department of Health and Social Care (DHSC) has invested funding of £10 million through the Innovate UK, together with China Ministry of Science and Technology (MoST)'s 5 million RMB investment, to support research tackling AMR. One of the projects (CHAT-COPD) will focus on using a patented herbal remedy Shufeng Jiedu® to aid antibiotic use reduction in exacerbation of Chronic Obstructive Pulmonary Disease. This herbal remedy is also one of those preparations recommended in the recently issued Chinese National COVID-19 Diagnostic and Treatment Guideline [34] - Chinese medicine for prevention of COVID-19 was issued in 23 provinces early on in the pandemic [35].

Changing public attitudes together with increasing awareness of the critical importance of an individual's responsibility to dealing with infection has become critical during the COVID-19 outbreak. Self-help techniques to prevent and minimise the risks of infection are key, and should always include washing hands in soap and water. Before the outbreak, the College of Medicine (<https://collegeofmedicine.org.uk/>) held a 1-day seminar and launched its initiative on 'Before we really need antibiotics – what are the healthy alternatives?' Based on evidence and cost they developed a resource that explored avoiding antibiotics by using traditional home remedies (herbals, essential oils, and supplements) for the prevention and management of everyday common infections including; cold, flu, sore throat, earache, sinusitis, cough, and urinary tract infection. They also focused on the evidence which can build host resistance, lifestyle advice, and the use of probiotics where antibiotics are not appropriate.

9. Conclusion

AMR is universal, affecting anyone and everyone, at any age and in any country and misuse is worsening the situation globally. Urgent action is needed and must involve government intervention and even restricting inappropriate access [36]. Public health education and changes in behaviour are critical as we begin to enter a post-antibiotic era where the simplest of infections will kill, as we only know too well with COVID-19.

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Author Contribution

NR had the initial concept. XYH, ML and NR worked together to develop and draft the manuscript.

Declaration of Competing Interest

XYH and ML are involved in research on AMR at the University of Southampton however the authors have no conflict of interests to declare regarding this article. NR is the Editor in Chief of the European Journal of Integrative medicine.

References

- [1] R.I. Aminov, A brief history of the antibiotic era: lessons learned and challenges for the future, *Frontiers in microbiology* 1 (2010) 134, <https://doi.org/10.3389/fmicb.2010.00134> Frontiers Media SA.
- [2] J. Davies, D. Davies, Origins and Evolution of Antibiotic Resistance, *Microbiol Mol Biol Rev.* 74 (September (3)) (2010) 417–433, <https://doi.org/10.1128/MMBR.00016-10>.
- [3] R.J. Fair, Y. Tor, Antibiotics and Bacterial Resistance in the 21st Century, *Perspect Medicin Chem.* 6 (2014) 25–64, <https://doi.org/10.4137/PMC.S14459> Published online 2014 Aug 28.
- [4] C.L. Ventola, The antibiotic resistance crisis: part 1: causes and threats, *P T.* 40 (4) (2015) 277–283.
- [5] WHO | Antimicrobial resistance, WHO, World Health Organization, 2018 Available at: <http://www.who.int/mediacentre/factsheets/fs194/en/> (Accessed: 27 March 2018).
- [6] A.Y. Peleg, D.C. Hooper, Hospital-acquired infections due to gram-negative bacteria, *The New England journal of medicine* 362 (19) (2010) 1804–1813, <https://doi.org/10.1056/NEJMra0904124> NIH Public Access.
- [7] S. Shaikh, et al., Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment, *Saudi journal of biological sciences* 22 (1) (2015) 90–101, <https://doi.org/10.1016/j.sjbs.2014.08.002> Elsevier.
- [8] C.L. Ventola, The antibiotic resistance crisis: part 1: causes and threats, P & T: a peer-reviewed journal for formulary management 40 (4) (2015) 277–283 MediMedia, USA, Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25859123> (Accessed: 16 September 2016).
- [9] J. O'Neill, Tackling drug-resistant infections globally: final report and recommendations the review on antimicrobial resistance, (2016) Available at: <https://amr-review.org/Publications> (Accessed: 29 September 2016).
- [10] A. Ghafur, Overconsumption of antibiotics, *The Lancet Infectious Diseases.* 15 (4) (2015) 377.
- [11] J. O'Neill, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, *Review on Antimicrobial Resistance* (December) (2014) 1–16.
- [12] WHO | Antimicrobial resistance, WHO, World Health Organization, 2016 WHO | What is antimicrobial resistance? (2016) WHO. World Health Organization.
- [13] World Health Organization, The evolving threat of antimicrobial resistance: options for action, *World Health Organization*, 2012.
- [14] D. Jasovský, J. Liitmann, A. Zorzet, O. Cars, Antimicrobial resistance—a threat to the world's sustainable development, *Upsala Journal of Medical Sciences* 121 (3) (2016) 159–164, <https://doi.org/10.1080/03009734.2016.1195900> Taylor & Francis.
- [15] B. Aslam, W. Wang, M.I. Arshad, S. Muzammil, M.H. Rasool, et al., Antibiotic resistance: a rundown of a global crisis', *Infection and Drug Resistance* 11 (2018) 1645–1658, <https://doi.org/10.2147/IDR.S173867>.
- [16] N. Jackson, L. Czaplewski, L.J.V. Piddock, Discovery and development of new antibacterial drugs: learning from experience? *Journal of Antimicrobial Chemotherapy* 73 (6) (2018) 1452–1459, <https://doi.org/10.1093/jac/dky019>.
- [17] G.D. Wright, Antibiotic resistance: what more do we know and what more can we do? *BMC biology* 11 (2020) 51, <https://doi.org/10.1186/1741-7007-11-51> BioMed Central <https://bmcbiol.biomedcentral.com/articles/10.1186/1741-7007-11-51>.
- [18] Public Health England, Guidance for managing common infections, including upper and lower respiratory, and urinary tract infections, 2 August (2019) <https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care>.
- [19] UK One Health Report Joint report on antibiotic use and antibiotic resistance, 2013–2017, (2019) Published.
- [20] L.J. Shallcross, D.S. Davies, Antibiotic overuse: a key driver of antimicrobial resistance, *Br J Gen Pract* 64 (629) (2014) 604–605, <https://doi.org/10.3399/bjgp14X682561>.
- [21] J. O'Neill, Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste, *The Review on Antimicrobial Resistance* [Internet]; (2015) [cited 2019]. Available from: (2015) <https://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf>.
- [22] C. Manyi-Loh, et al., Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications', *Molecules* 23 (4) (2018) 795, <https://doi.org/10.3390/molecules23040795>.
- [23] T.P. Van Boeckel, S. Gandra, A. Ashok, Q. Caudron, B.T. Grenfell, S.A. Levin, R. Laxminarayan, Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data, *The Lancet Infectious Diseases* 14 (8) (2014) 742–750.
- [24] UKRI, India-UK Tackling AMR in the Environment from Antimicrobial Manufacturing Waste, [Internet]; 2019 [cite 2019]. Available from: (2019) <https://nerc.ukri.org/research/funded/programmes/uk-india-amr/news/>.
- [25] P. Little, B. Stuart, F.D. Hobbs, M. Moore, J. Barnett, D. Popoola, K. Middleton, J. Kelly, et al., An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial, *The Lancet.* 386 (10004) (2015) 1631–1639, [https://doi.org/10.1016/S0140-6736\(15\)60127-1](https://doi.org/10.1016/S0140-6736(15)60127-1).
- [26] P. Little, S. Turner, G. Warner, M. Moore, J.A. Lowes, H. Smith, C. Hawke, M. Mulle, Developing clinical rules to predict urinary tract infection in primary care settings: sensitivity and specificity of near patient tests (dipsticks) and clinical scores, *The British Journal of General Practice: the Journal of the Royal College of General Practitioners* 56 (529) (2006) 606–612.
- [27] Paul Little, Michael Moore, et al., Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management), *BMJ* 347 (2013) f5806, <https://doi.org/10.1136/bmj.f5806>.
- [28] P. Little, I. Williamson, G. Warner, C. Gould, M. Gantley, A.L. Kinmonth, Open randomised trial of prescribing strategies in managing sore throat, *BMJ* 314 (7082) (1997) 722–727, <https://doi.org/10.1136/bmj.314.7082.722>.
- [29] G20 Leaders' Declaration: Building Consensus for Fair and Sustainable Development, (2019) [Internet]; 2018 [cite 2019]. Available from: <http://www.g20.utoronto.ca/2018/2018-leaders-declaration.html>.
- [30] T.F. Landers, et al., A review of antibiotic use in food animals: perspective, policy, and potential, *Public health reports* (Washington, D.C. : 1974) 127 (1) (2012) 4–22, <https://doi.org/10.1177/003335491212700103> SAGE Publications.
- [31] WHO | Herbal medicine research and global health: an ethical analysis, WHO. World Health Organization, 2011.
- [32] S. Gibbons, Plants as a Source of Bacterial Resistance Modulators and Anti-Infective Agents, *Phytochem Rev.* 4 (1) (2005) 63–78 [Internet]. Kluwer Academic Publishers; 2005 Jan [cited 2016 Oct 12] Available from: <http://link.springer.com/10.1007/s11101-005-2494-9>.
- [33] Integrative health care | Primary Care | University of Southampton, (2020) <https://www.southampton.ac.uk/primarycare/research/integrative-health-care.page>.
- [34] L.T.F. Ho, K.K.H. Chan, V.C.H. Chung, T.H. Leung, Highlights of traditional Chinese medicine frontline expert advice in the China national guideline for COVID-19, *European Journal of Integrative Medicine.* (2020) 101116.
- [35] H. Luo, Q.-L.-L. Tang, Y.-X.-X. Shang, S.-B.-B. Liang, M. Yang, N. Robinson, J.-P.-P. Liu, Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs, *Chin J Integr Med* 26 (4) (2020) 243–250, <https://doi.org/10.1007/s11655-020-3192-6>.
- [36] R. Laxminarayan, P. Matsoso, S. Pant, et al., Access to effective antimicrobials: a worldwide challenge, *Lancet* 387 (10014) (2016) 168–175, [https://doi.org/10.1016/S0140-6736\(15\)00474-2](https://doi.org/10.1016/S0140-6736(15)00474-2).