Personal View

Global antimicrobial stewardship and the need for pharmaceutical system strengthening for antimicrobials within a One Health approach

Rocio Villacorta Linaza^{1*}, Chantelle Genovezos², Timothy Garner¹, Edwin Panford-Quainoo¹, Adam P. Roberts¹

Addresses

¹ Department of Tropical Disease Biology, Liverpool School of Tropical Medicine, Pembroke Place, L3 5QA, UK

² Hypha Group Limited, 320 Firecrest Court, Centre Park, Warrington, UK, WA1 1RG, UK

*Corresponding

Abstract

Objectives

The Covid-19 pandemic has highlighted both the vulnerabilities and the critical role of global pharmaceutical systems in enabling equitable access to medicines. In this personal view, we position the pharmaceutical system as a missed research and investment opportunity that, if integrated properly, would benefit antimicrobial stewardship (AMS) programmes within a One Health approach.

Key findings

The pharmaceutical supply management cycle (PSMC) illustrates the continuous interdependence between four key phases - selection, procurement, distribution and use. Furthermore, a PSMC is subject to external forces of market competition, policy and regulation – across human, animal and environmental health. We present examples of overlap in PSMCs across different One Health sectors and discuss the need for integration within human, animal and environmental health contexts.

Summary

Despite pharmaceutical systems being fundamental to successful AMS programmes they are currently neglected and undervalued. Research and investment into pharmaceutical system optimisation and integration into AMS programmes presents an opportunity for countries, both high-income countries (HICs) and low- and middle-income countries (LMICs), to develop responsible, comparable and global AMS innovations and interventions.

Keywords

Medicines management, Pharmaceutical Public Health, Anti-infectives and Drug utilization.

The need for strengthening pharmaceutical systems has most recently been highlighted by the global response to COVID-19. The main objectives of a pharmaceutical system are to: provide access to medicines and supplies, encourage their rational use, and ensure their quality, safety, and efficacy [1]. The global pandemic has uncovered vulnerabilities in national pharmaceutical systems of HICs and enlivens the debate on equity of access to medicines, vaccines and health technologies for LMICs. Following the rapid development and manufacturing of COVID-19 vaccines, equitable access for every country is being made possible through global collaboration [2]. Yet even with targeted global distribution efforts, supply challenges, even within HICs such as the UK, have threatened to disrupt COVID-19 vaccine programmes [3].

The pressure of the pandemic on health systems has forced health authorities to explore diverse treatment options. Under discussion in the health community are both short- and long-term impacts on the rest of the health system, including the changing use of antimicrobials in hospitals and communities as a result of the COVID-19 pandemic [4]. Where access to antimicrobials is limited, particularly in LMICs, this has a greater impact on national abilities to respond to COVID-19 related secondary infections and other infectious diseases. The United States Food and Drug Administration (FDA) issued an emergency use authorisation (EUA) permitting chloroquine phosphate (medical grade) and hydroxychloroquine sulfate to be added to the strategic national stockpile (SNS) [5]. Furthermore, existing drugs have been trialled for effectiveness against COVID-19, such as the controversial use of ivermectin (IVM) [6] and the common prescribing of azithromycin (AZT) [7]. Prescribing AZT for COVID-19 necessitates increased manufacturing of the drug to cover all treatment needs. Furthermore, with an abundance of information communicated daily by the media and available on the internet, people at home may feel encouraged to obtain drugs that are highlighted in news headlines. For example, in some countries, drugs like IVM can be easily obtained for veterinary use without prescription. These two examples highlight how the pharmaceutical systems can overlap and raises questions on appropriate antimicrobial stewardship (AMS) and the impact on antimicrobial resistance (AMR).

Implementation of AMS programmes is dependent on the existence of a reliable pharmaceutical system. The pharmaceutical system is a sub-system of the health system, which operates through the interconnectivity of multiple management systems and further sub-systems [8]. Changes in one system can trigger changes in others with this interaction playing out at national and global levels.

The *Pharmaceutical Supply Management Cycle (PSMC)* (Figure 1) is a key component of the pharmaceutical system. The PSMC operates like a wheel, where each component of the management support system is essential to making movement through the cycle possible. Subsequently, if one of the management support systems does not function the wheel does not turn, and the cycle is disrupted. Central to PSMC are management support, policies, and legal frameworks, which interlink to enable effective management of the pharmaceutical system. Effective management makes a crucial difference in all aspects of the pharmaceutical system [8].

Figure 1: Pharmaceutical Supply Management Cycle (PSMC)

The figure depicts the continuous cycle of supply management, highlighting the interdependence between four key phases - selection, procurement, distribution and use, and their relationship with external forces of market competition, policy and regulation.

Achieving the right supply conditions is influenced by several factors that traverse human, animal, and environmental health, more recently recognised as One Health [9]. If we take a pharmaceutical systems view of a One Health approach to AMS, we can recognise the separate and overlapping supply management cycles (Figure 2), with each of the health sectors circulating through a process of selection, procurement, distribution and use, in varying supply market competition and government regulatory frameworks (Figure 2).

Figure 2 title: Pharmaceutical systems of a One Health approach

This figure illustrates the interconnection between the human, animal and environmental aspects of a One Health approach, the pharmaceutical supply management cycle which exists within the background of each of the three aspects, and a question mark placed where there is potential overlap for intervention opportunities.

Greater focus on One Health interventions, relevant to these objectives and specifically PSMC, would lead to more effective and globally integrated AMS and more resilient national health systems. If stewardship of antimicrobials within a One Health approach is not robust, inappropriate or restricted antimicrobial choices may result, exacerbating AMR. AMR does not distinguish between LMICs and HICs and it is often more consequential in the former where health systems are overburdened, lack resources and are less able to respond to challenges as a result of AMR. Nonetheless, for AMR interventions to be effective in any country both global responsibility and local accountability for a One Health approach is required.

To-date efforts to tackle AMR have focused on consumption patterns and data collection, such as Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS) [10] and national surveillance systems which themselves report to Global Antimicrobial Resistance Surveillance System (GLASS) [11]. Academic activities have focused on determining the drivers of resistance, cycling and combining antibiotics, development of new drugs and alternative treatment such as bacteriophage therapy, public and patient engagement, continuous professional development (CDP) for prescribers and, looking forward, there are prospects for the gene editing technology CRISPR. Pharmaceutical systems are currently a neglected and undervalued aspect of AMS programmes. They do not attract interest like clinical work and emerging technologies do and yet, are foundational to successful AMS.

We posit the pharmaceutical system should also be considered in AMS strategies in order to address AMR. Evidence for interventions that challenge the pharmaceutical system within a One Health approach are limited. A recent systematic review of evidence from human and animal health systems in LMICs found that ‘supply chains’ are tackled in only 1 out of more than 70 (1.5%) of AMR interventions [12].

Targeted research into pharmaceutical systems is an opportunity for AMS programmes to analyse and strengthen implementation of an overarching One Health approach to tackle AMR. It is a core area where human, animal, and environmental health overlap and it requires understanding how, and to what extent, it is an enabler or barrier to AMS interventions. In line with a One Health approach, optimising the use of antimicrobials is defined by the World Health Organisation (WHO) in their Global action plan on AMR 2015 (Objective 4) [13]. AMS programmes have been developed across both LMICs and HICs to support the implementation of this objective. AMS represents one of three “pillars” of an integrated approach to health systems strengthening (HSS) [13] the other two being Infection Prevention and Control and Patient Safety. Core to HSS are six “building blocks” defined by WHO. The pharmaceutical system is a fundamental sub-system [14] to the WHO building block (iv) access to essential medicines, vaccines and technologies.

In LMICs, the lack of market availability of antimicrobials and the inadequate management of supply, limits the choice of antimicrobials that can be prescribed. Whilst countries have limited control or influence on market availability, there is responsibility and accountability for supply management. Examples include quantification and procurement, stock control (e.g. managing expiry), storage conditions, and security. Where supply of antimicrobials is limited, sporadic, and/or inadequately managed, countries may face difficult choices in the use of available antimicrobials. Examples include treating animals versus humans, and prioritising use of donated medicines.

In HICs gathering consumption data is used to inform AMS policy and strategy, however in LMICs the systems, tools, and human resources to capture and analyse data are often sporadically available and/or not in place. For LMICs, strengthening the health system through its pharmaceutical system is a critical need as pharmaceuticals represent an estimated 30 to 50 percent of health budget [15]. In order to achieve this, experts from a variety of fields including economics, management, pharmacy, chemistry, medical, legal and logistics [16] need to be involved. In particular, there is a need to work

collaboratively to ensure the effective coordination and functioning of each cycle in pharmaceutical supply management [16].

Research and investment are required into innovative strategies that achieve these objectives and better manage supply cycles, particularly in LMICs and specifically through a One Health lens. Innovation need not only be new technology, it could also be taking existing strategies from different sectors and applying them in new contexts. This need is even more critical, whether facing the rapid onset of a new pandemic such as COVID-19 or a persistent, growing and severe crisis such as AMR. The systems also need to be robust enough, with adequate redundancy, to be able to cope with unforeseen events such as the most recent blockage of the Suez Canal. By focussing on PSMC as a common need with shared risks across a One Health landscape, investigations should highlight opportunities for collaboration across human, animal and environmental health, uses of technology such as blockchain, and overall strengthening of AMS programmes through more effective interventions. Therefore, a pharmaceutical systems view of One Health should be integrated into AMS approaches to tackle AMR.

References

1. World Health Organization Bigdeli M, Peters D.H, Wagner A.K. 2014. Medicines in Health Systems: Advancing access, affordability and appropriate use. <https://apps.who.int/iris/handle/10665/179197> (20 April 2021, date last accessed).
2. Global Alliance for Vaccines and Immunisation. 2021. <https://www.gavi.org/vaccineswork/covax-explained> (20 April 2021, date last accessed).
3. Torjesen I. 2021. Covid-19 vaccine shortages: what is the cause and what are the implications?. British Medical Journal. <https://doi.org/10.1136/bmj.n781>
4. Rodríguez-Baño J, Rossolini G.A, Schultsz C, Tacconelli E, Murthy S, Ohmagari N, Holmes A, Bachmann T, Goossens H, Canton R, Roberts A.P, Henriques-Normark B, Clancy C.J, Huttner B, Fagerstedt P, Lahiri S, Kaushic C, Hoffman S.J, Warren M, Zoubiane G, Essack S, Laxminarayan R, Plant L. 2021. AMR research in a post-pandemic world: Insights on antimicrobial resistance research in the COVID-19 pandemic. Transactions of The Royal Society of Tropical Medicine and Hygiene. <https://doi.org/10.1016/j.jgar.2021.02.013>.
5. U.S Food and Drug Administration. Letter of Authorization - chloroquine phosphate and hydroxychloroquine sulfate. 28 March 2020. <https://www.fda.gov/media/136534/download> (20 April 2021, date last accessed).
6. Jimenez D. Ivermectin and Covid-19: how a cheap antiparasitic became political. Pharmaceutical Technology. 19 Apr 2021. <https://www.pharmaceutical-technology.com/features/ivermectin-covid-19-antiparasitic-political/> (20 April 2021, date last accessed).
7. Bookwalter C.M. Drug Shortages Amid the COVID-19 Pandemic. U.S Pharmacist. 12 February 2021. <https://www.uspharmacist.com/article/drug-shortages-amid-the-covid19-pandemic> (20 April 2021, date last accessed).
8. Management Science for Health. 2014. MDS-3: Managing access to essential medicines and health technologies. 2014. <https://www.msh.org/sites/default/files/mds3-jan2014.pdf> (20 April 2021, date last accessed).

9. Kahn L.H. 2017. Antimicrobial resistance: a One Health perspective. Transactions of The Royal Society of Tropical Medicine and Hygiene. <https://doi.org/10.1093/trstmh/trx050>
10. The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS). 2021. <https://www.global-pps.com/ourproject/> (20 April 2021, date last accessed).
11. World Health Organization. Global Antimicrobial Resistance Surveillance System. 2015. <https://www.who.int/glass/en/> (20 April 2021, date last accessed).
12. Wilkinson, A., A. Ebata, and H. MacGregor. 2018. Interventions to Reduce Antibiotic Prescribing in LMICs: A Scoping Review of Evidence from Human and Animal Health Systems. Antibiotics (Basel). Doi: 10.3390/antibiotics8010002
13. World Health Organization. 2015. Global action plan on antimicrobial resistance. https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1 (20 April 2021, date last accessed).
14. World Health Organization. .2007. Everybody business: strengthening health systems to improve health outcomes : WHO's framework for action. World Health https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1(20 April 2021, date last accessed).
15. Cambridge, MA: Management Sciences for Health. 2010. Health Systems in Action: An eHandbook for Leaders and Managers. <http://www.msh.org/resources/health-systems-in-action-an-e-handbook-for-leaders-and-managers> (22 April 2021, date last accessed).
16. Villacorta Linaza, R. 2009. Bridging the gap: the role of pharmacists in managing the drug supply cycle within non-governmental organizations. The International Journal of Health Planning and Management. <https://doi.org/10.1002/hpm.1023>