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

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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 both high income countries and low- and middle-income countries, to develop responsible, comparable and international 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 high-income countries (HICs) and enlivens the debate on equity of access to medicines, vaccines and health technologies for low- and middle-income countries (LMICs). For vaccine access to combat COVID-19 there has been global collaboration through COVAX, which has sought to provide equal access for participating countries regardless of income levels [2]. Yet even with global intention to collaborate, supply challenges, within HICs such as the UK, threatened to disrupt roll-out of COVID-19 vaccines [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]. National responses to COVID-19 related secondary infections, and other infectious diseases, requires access to and supply management of antimicrobials including mitigating the risk of short supply. For example, the United States Food and Drug Administration (FDA) issued an emergency use authorisation (EUA) permitting chloroquine phosphate (medical grade) and hydroxychloroquine sulphate 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. AZT has not been the only antimicrobial under pressure. In the UK there was a shortage of IV co-amoxiclav and at one point IV clarithromycin was also at risk. Given the co-amoxiclav shortages, many hospitals switched to cephalosporins to treat bacterial pneumonia (although evidence demonstrates overtreatment). This sweeping change in practice subsequently led to pressure on the supplies of cefuroxime and ceftriaxone in particular [8]. 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. Pre-pandemic issues also serve as examples of fragile supply chains. In 2017 there was a global shortage of piperacillin-tazobactam following an explosion at the only factory making the active pharmaceutical ingredient (API). This resulted in system-wide changes to how resistant infection is treated [8]. There have also been shortages in the manufacture and supply of IV co-trimoxazole [8] and mupirocin (Bactroban) [9], that can impact on patient care. These 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 are dependent on the existence of a reliable pharmaceutical system, which is a pillar for any health programme. COVID-19 vaccines and antimicrobial supply are prominent examples, amongst many others. The pharmaceutical system is a sub-system of the health system, which operates through the interconnectivity of multiple management systems and further sub-systems [10]. 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 the 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 [10].
Figure 1 title: Pharmaceutical Supply Management Cycle (PSMC)
Figure 1 legend: The figure depicts the continuous cycle of supply management, highlighting the interdependence between four key phases - selection, procurement, distribution and use, as well as, the 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 [11]. A One Health approach is defined by the World Health Organisation (WHO) as "an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes" [12]. A One Health Approach is particularly useful when investigating AMR [11] as the drivers for the emergence of AMR may well be e.g. within the agriculture (animal health) sector, and which ultimately affect treatment options for human disease (within the human health sector) [13,14] as has been recently demonstrated for transferable colistin resistance driven by the use of colistin as an antimicrobial growth promoter for pig production in China [15]. Moreover, a One Health approach to tackling AMR was discussed and agreed upon at the recent G7 summit in the UK, as described in both the G7 Carbis Bay Health Declaration and the G7 Health Ministers' Communique which preceded it [16,17]. 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
Figure 2 legend: The 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. The circles are schematically the same size in the diagram but likely are not equally weighted in terms of volume of supply.

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) [18] and national surveillance systems, which themselves report to Global Antimicrobial Resistance Surveillance System GLASS [19]. 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. Importantly the way antibiotics are developed, bought and sold is in transition. Over the counter (OTC) and internet sales of antibiotics, both appropriate and inappropriate, are increasing [20,21,22] and efforts to regulate this will benefit from robust and trackable supply chain systems. Moreover, due to the changing funding landscape of antibiotic research and development, itself due to a broken economic model of return on investment

[23,24,25], we are likely to see changes in supply based on innovative mechanisms of R&D funding and sales of antibiotics, e.g. the implementation of fixed fee payments to antimicrobial producers by the UK and Swedish governments [26,27]. Stewardship and equitable access of new antibiotics being pulled through the development pipeline will be dependent on agile and integrated pharmaceutical supply chains.

We posit therefore that 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 is limited. A recent systematic review of evidence from human and animal health systems in LMICs found that 'supply chains' were within the scope of only 1 out of more than 70 (1.5%) of AMR interventions [28]. Targeted research into pharmaceutical systems is an opportunity for AMS programmes to analyse and strengthen implementation of an overarching One Health approach to tackling 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 WHO in their Global action plan on AMR 2015 (objective 4) [29]. 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) [29] 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 [30] 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 a need to strength responsibility and accountability for supply management. Examples include quantification and procurement, stock control (e.g., managing expiry), storage conditions, and security, as well as quality assurance and control measures across procurement and supply chain management. International instruments (guidelines) on the use of antimicrobials across One Health have been captured by the tripartite partnership between WHO, the Food and Agriculture Organization (FAO) and Office International des Epizooties (OIE) [31]. Whilst guidance is available the question remains how to ensure consistent and effective implementation amongst social, technological, economic, environmental, political, and legal challenges. 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 [32]. In order to achieve this, experts from a variety of fields including economics, management, pharmacy, research and development, medical, legal and logistics [33] 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 [33].

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 it in new contexts. Such possibilities require greater exploration to identify how they could apply and where they would be most effective. AMS interventions using a One Health approach have been demonstrated to promote understanding on antimicrobial use and resulted in improved health facility and community practices [34]. Such projects could be further enhanced through widening scope to encompass the full PSMC.

Addressing the full scope of PSMC in One Health 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.

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