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PERSPECTIVE

Phage therapy: resurrecting a historical solution for the contemporary challenge of rising antibiotic resistance in Latin America

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ABSTRACT

Introduction: Antimicrobial resistance in Latin America is a growing concern in both human and non-human animal populations. The economic burden that is likely to be imposed through increased resistance will cause further strains on public health systems and the population at large.

Areas covered: We propose the rapid adoption and implementation of phage therapy as a necessary addition to the medical arsenal to help mitigate antimicrobial resistance, with an emphasis on considering the potential benefits that highly biodiverse countries such as Ecuador may have on phage discovery. However, programs may count on limited government support and/or facilitation, which could slow progress.

Expert opinion: We highlight the need for educational campaigns to be implemented in parallel with the development of phage therapy programs, particularly to implement these novel treatments in rural and indigenous communities.

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1. Introduction

Antimicrobial resistance (AMR) persists as a top public health threat. In Latin America, mis-regulated administration of antibiotic use has acutely exacerbated the rise of antibiotic resistance which is evolving simultaneously in aquaculture and/or agricultural livestock, and medical institutions and the community at large [1]. While countries in Latin America such as Ecuador are keenly aware of the risks resistance poses, public health institutions remain sluggish to recover from the global COVID-19 pandemic, leaving the economic pressures predicted to be brought about by antimicrobial resistance [2] a persistent risk capable of being economically crippling. Increased regulatory policies and improved antibiotic stewardship are obvious and necessary first steps [3], yet an incomplete strategy to comprehensively address increasing resistance. We highlight Ecuador as a small country suitable for a pilot program, where local teams are familiar with these issues, yet have the capacity to address them in a broadly applicable way.

Despite consistent warnings, AMR in Latin America has reached critical levels. Gram-negative bacteria resistant to carbapenem has increased from 0.3% in 2002 to 21% in 2016, with some countries reporting frequencies of 20%–50% [4]. Data from Ecuador show that 44 hospitals are currently surveilling the presence of AMR resistant infections, isolating strains from medical care facilities [4]. They report particular concerns from *Escherichia coli*, and also list *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Enterococcus faecalis* and *Serratia marcescens* [4]. *Escherichia coli* has evolved resistance to many so-called drugs of last resort, for example carbapenems where resistance is reported in up to 50% of strains to carbapenems, in addition to strains with MCR-1 derived resistance to colistin. *Staphylococcus aureus* isolates displayed resistance to penicillin (87%) and cefazolin (60% [4]). Similarly, resistant *Klebsiella pneumoniae* strains are found in up to 55% in ICU infections, and resistant *Pseudomonas aeruginosa* cases upwards of 30% [4].

Increasing AMR bears significant economic costs. According to the World Bank, the reduction in labor supply due to premature mortality caused associated with microbial resistance will result in global costs between 1.2% and 4.1% of worldwide GDP [5]. Increased frequencies of antimicrobial resistance could cause low-income countries to lose more than 5% of GDP and push 28 million people, mostly in lower- and middle-income countries (LMIC), into poverty by 2050 [6]. Treating patients with multidrug-resistant microorganism (MDR) infections with prolonged hospital stays augments the cost of medical attention [6]. Effects on low-income countries are enhanced due to the lack of access to resources and medicines to address the problem [7], which can make procedures riskier and more costly, disproportionately encumbering LMIC that already have fragile health systems [8]. For example, without effective antibiotics, mortality rates caused by infections following hip surgery could increase by up to 30% [9]. AMR can also have negative impacts beyond health systems. Concerns are elevated related to agricultural production, which can affect the economy of LMIC that mainly depend on this economic activity such as Ecuador.

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Article highlights

- Antimicrobial resistance in Latin America is a growing concern in both human and non-human animal populations
- The economic burden that is likely to be imposed by increased resistance will cause further strains on public health systems and the population at large
- We propose the rapid adoption and implementation of phage therapy as a necessary addition to the medical arsenal to help mitigate antimicrobial resistance, with an emphasis on considering the potential benefits that highly biodiverse countries such as Ecuador may have on phage discovery
- However, programs may count on limited government support and/or facilitation, which could slow progress
- We highlight the need for educational campaigns to be implemented in parallel with the development of phage therapy programs, particularly to implement these novel treatments in rural and indigenous communities

Recent epidemiology reviews have shown that bacterial resistance to carbapenems continues to increase in Latin America, which includes cases of co-expression of different carbapenem class resistance found in a single patient [10]. This troublesome scenario suggests a potential future whereby no antimicrobial therapies will be available for some patients. In light of this a Latin America consortium has been founded to deal with multi-resistant pathogens (*Concenso latinoamericano para definir, categorizar y notificar patógenos multirresistentes y con resistencia extendida o panresistentes* [11]) whose aim is to homogenize terminology of multi drug resistant strains to facilitate timely diagnoses. Unfortunately, to date, widespread utilization appears to be falling short of expectations. Poor adoption could be in part attributable to low investments of governments in such public health initiatives. Still other initiative such as the Antimicrobial stewardship (ATS) programs assist to control the use and promote the optimization of antibiotics. Although adoption appears to be increasing, they remain underutilized, and we would benefit from better evaluations to determine whether they have been effective in reducing infections. Ultimately, such programs should be the cornerstone for the controlled use of antimicrobials in Latin America, however without readily available data between countries with similar public health programs it remains difficult to replicate effective strategies, which diminishes the possibility to have regional collaborative agreements in the controlled use of antibiotic therapies.

The acute challenge of tackling antibiotic resistance is further accentuated by a recent 40% spike in global antibiotic consumption from 2000 to 2010 and the imprudent prescription habits, has driven the development of multiple strategies to track resistance [12]. Alternatives available, but not implemented widely in Latin America include PoOf-Care (POC) tests for precise diagnosis, wearables for early detection, mobile connectivity to reach remote regions, AI-powered diagnoses, and various platforms like Near POC, True POC, and Instrument-Free Platforms that offer innovative treatments and diagnostics [13,14]. While these tools will provide improved diagnosis, the economics could be prohibitive in many regions of LMIC. Ultimately, countries would be best served by a combined approach of utilization of new technologies (when possible/feasible) and expanded stewardship and education could contribute to reducing the severity of AMR. However, novel/alternative antimicrobials are still needed to address existing AMR and, ideally, reverse the trajectory.

Therefore, in light of the current trajectory of AMR, we highlight the potential contributions of phage therapy as an ideal addition to contribute to the mitigation of this problem [15]. Phage therapy involves the use of lytic phages to infect and lyse bacteria at the site of infection. Phages are highly host-specific and can be used in combination with antibiotics to address AMR bacterial infections, causing less disruption to patient microbiomes compared to antibiotics [16]. Phage therapies can be developed and implemented rapidly, and at relatively low costs [17]. Additionally, phages can be acquired from environmental sampling to identify novel types, where treatments can be tailored in response to regionally abundant AMR strains, therefore representing a much more agile solution to treatment of infections than the development of novel traditional antibiotics. Urgent and concerted investment in research, and the development of better alternative biological treatments such as phage therapy are needed to accelerate more equitable access to effective treatments for bacterial infections.

The infrastructure necessary to support the widespread adoption of phage therapy in Latin America is currently inadequate, or in many instances absent. We therefore encourage relevant authorities to recognize the urgency of the AMR issue, and allocate resources toward the development and implementation of phage therapy and other novel antimicrobials. This would require improved research infrastructure and broad scale educational campaigns to ease the implementation of less-traditional medical treatments. Outreach programs will need in urban communities, however programs specifically designed to reach rural and indigenous communities will be especially necessary to promote adoption. Considerable resistance should be anticipated; therefore, education should proceed treatment implementation, to raise awareness about the benefits of adopting phage therapy, to mitigate resistance directed toward the treatment method [18].

Although no contemporary empirical evidence from the broad-scale application of phage therapy in Latin America is available, early implementation in Brazil showed enormous promise for several decades after its first implemented in 1923, before its unexplained disappearance [19]. Therefore, given previous successes, governments should consider investing in phage therapy as an economically viable option to address the costly preexisting problem of antibiotic resistance, as the long-term benefits of such an investment would far outweigh the initial short-term costs. Additionally, permitting and incorporating compassionate use of phage therapy (cPT) until broadscale operations can be implemented would be beneficial to begin treatments and familiarize government agencies, medical professionals, researchers and patients with the method [20]. The *de novo* implementation of phage therapy is not without challenges [21]. However, establishing local laboratories capable of meeting the screening, characterization, and standardized phage production methods following appropriate pharmaceutical regulations/protocols can be achieved, requiring training of staff and only slight modifications to existing laboratories.

Phage therapy would be of great value to LMIC where relevant phages can be sourced and processed locally and efficiently [22], particularly in highly biodiverse regions such as Ecuador. The overall rich biodiversity in Latin America coupled with ecological diversity of regions with human settlements has been largely untapped for phage discovery, were these countries to prove hotspots in phage diversity then important phage additions, ranging from generalists though specialist, could contribute to broader cocktails [23]. Furthermore, the local discovery and development of phage-based therapeutics is an empowering mechanism which contributes to the democratization of medicine. Notwithstanding, nationwide implementation will require ministry of health approval and the establishment research laboratories, and a non-insignificant capital investment. Fortunately, we can build upon the development of the international phage therapy field to focus on local acceptance and deployment. Although laboratories could be rapidly outfitted, implementation may be hindered by government regulations, and therefore while we require direct funding/logistical support, at minimum implementation will require indirect governmental support in facilitating regulations. For example, standardized protocols for the safe manufacture and packaging of phage-based therapeutics approved by ministries of health will be essential for widespread development and deployment. These protocols could be modeled after those currently being developed in the U.S.A. and European Union based on decades of prior use. Next, standardized limits for host cell protein and other trace components in preparations will need to be determined and enforced. Once more, these can be based upon existing limits for pharmaceutical products. Adherence to these standards will allow responsible phage-based pharmaceutical production in Latin America and demonstrate supportive government response to a public health emergency.

An attractive advantage for clinical use of phages is their ability to act in synergy both with one other, as well as in conjunction and with antibiotics, which can enhance therapy precision [24]. A 2020 systematic review of the efficacy of phage therapy analyzed all clinical trials (59 good-quality studies with a total of 2,241 patients) comparing phage therapy with conventional antibiotic therapy and placebo trials [25]. The conclusions of this SR emphasize that phage therapy has a potential and promising benefit for treating difficult infections (77% of the cases had clinical improvement with phage therapy vs 55% with the therapeutic standard) and with few adverse effects (7% [26]).

Phage therapy is not without disadvantages. Phage purification is not necessarily trivial, and host specificity can make it difficult to identify the most effective phage for a particular bacterial strain, and in some cases *in vitro* activity may not be accurately reflected *in vivo* [27]. Thus, creating a phage-based therapy can require some personalization depending on the type of infection and the patient, potentially delaying administration of phage. Lastly, as phage therapy is still being studied clinically, potential side effects are still being determined, and the necessary pharmacokinetic and pharmacodynamic studies are still being performed to ensure patient safety. However, their extensive use in East Europe, historic use in Brazil, and the recent deployment of them in the U.S.A. and western Europe have not revealed any major side effects when utilized appropriately [19,28].

Phage therapy could be a powerful addition to treatment arsenals and an option to combat antimicrobial resistance in LMIC, since bacteriophages are relatively cheap and easy to produce [29]. However, more research is needed to assess the safety and efficacy of phage therapy in different settings, including low-income countries and diverse communities from urban to rural, including indigenous. Clinical trials that are underway are scarce, and most of them have been carried out in higher income countries. The results are promising, but more studies are needed as implementation expands geographically such as into Latin America.

1.1. Expert opinion

This article highlights the opportune timing for Latin American countries, such as we suggest a test case in Ecuador, to rapidly adopt, and broadly implement phage therapy techniques. With imminent challenges due to the rise of antibiotic resistance on the horizon, we urge governments to take multiprong actions to begin educating citizens on treatment strategies beyond traditional antibiotics, and to begin the development and implementation phage therapy programs. Yet educational campaigns will likely need to begin with the governments themselves before it can trickle downstream to both urban and remote communities. Therefore, we urge both the research and medical fields to unite and organize collaborative presuming an upstream facing effort. In conducting outreach to the public medical personnel must be aware of the inherent hesitation and distrust that are likely opinions held by members of more remote populations such as indigenous communities and be especially sensitive to how research and applications could be conducted across ethnically diverse communities.

The goal of mitigating potential unnecessary financial burdens on the healthcare system, and treating MDR infections is lofty, but attainable if investments are made rapidly. We propose that Ecuador in particular could be poised to be a regional reference, leading phage therapy treatments in coming years if political, medical and community support can be garnered quickly. Phage discovery would ideally be done in conjunction with undergraduate training in the field such as microbiology, affording ample opportunities for undergraduate researcher involvement. Such projects would be ideal to integrate in countries like Ecuador where public outreach (*vinculacíon con la comunidad*) involvement is a legal requirement for graduation, and students could seamlessly blend their research experience with public outreach projects, and even public health system personnel.

Just as many Latin American countries are renown as biodiversity hotspots in flora and fauna, the diversity of phages present in and around human populations similarly spans incredibly diverse ecosystems, and likely would become an incredible resource both for the continent as well as insular regions like Galapagos. Moreover, if levels of phage diversity remotely approximate the biodiversity found in other taxon, phage portfolios generated in these regions would be a huge asset to the international medical communities and reaffirm

the importance of conservation practices in all levels of biodiversity in the region. However, governments will need to classify phage therapy, whether they consider phages to be a drug (like in the United States) or a medical product (European Union) [28], or create a novel classification which would permit the legal grounds for large-scale production. Once categorized, phage therapy applications could begin in environmental, livestock (terrestrial and aquatic), and human populations.

We hold the optimistic viewpoint that the future of phage therapy is bright, shaped by rapid collaborative growth across geographic and political boundaries in the short-term future. Empowered communities will be able to isolate, characterize, and develop local solutions to local AMR strains by utilizing local biodiversity. Following established standards of production, retrofitted laboratories could produce safe and effective antimicrobials locally and quickly as a rapid response to the emergence of AMR, preventing novel strains from spreading worldwide. International cooperation and standardized protocols could allow for the simple and translatable production of newly discovered phages both regionally and internationally. As such, locally present biodiversity solutions will provide regional and international solutions to biomedical problems and expose future generations of scientists and health care professionals to drug development and reduce the need for reliance on externally developed antimicrobials.

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Declaration of interest

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