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Broad-spectrum therapeutics: A new antimicrobial class

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ABSTRACT

There are currently no emergency treatments for pandemics, yet drug repositioning has emerged as the foremost treatment development strategy for COVID-19, with an aim to identify successful antiviral therapeutics from safe, non-antiviral candidates. These therapeutics include antibiotics such as azithromycin and the antiparasitic nitazoxanide, both of which exhibit antiviral activity. Broad-spectrum therapeutics (BSTs) are a class of antimicrobials active against multiple pathogen types. Establishment of a developmental framework for BSTs will markedly improve global preparedness for future health emergencies.

1. Introduction

The discovery of the first antibiotic in 1928 was concomitantly a realisation that small molecule drugs could kill bacteria. In the decades since, the discovery of antifungal, antiparasitic, and antiviral agents expanded upon this principle and the 20th century saw the development of a vast array of small molecule antimicrobials, each specific for a given pathogen or pathogen class. In 2020, however, this paradigm was challenged by the SARS-CoV-2 pandemic, for which a plethora of antibiotics and antiparasitics were deployed against a viral disease. For the first time on a global scale, small molecule drugs were used outside of their original antimicrobial classification and the lack of therapeutics suitable for global health emergencies became evident (Pushpakom et al., 2019; Harrison, 2020).

We introduce the term broad-spectrum therapeutic (BST) to describe a class of antimicrobials active against multiple pathogen types. This term is derived from the Strategic Plan for Biodefense Research by the U.S. Department of Health and Human Services (HHS) and the National Institute of Allergy and Infectious Diseases (NIAID), which states that 'anti-infectives with broad-spectrum activity directed at common, invariable, and essential components of different classes of microbes could potentially be effective against both traditional and non-traditional threats' (Biodefense Strategic Plan, 2002; Biodefense Strategic Plan, 2007; NIH Funds Development of New Broad-Spectrum Therapeutics, 2015). The BST classification increases the speed at which potential emergency treatments are identified by removing the need to consolidate repositioning histories of antimicrobials after a health emergency has occurred; yet it also solidifies the importance of drug repositioning as a formidable mode of discovering new antimicrobial indications for existing therapeutics (Table 1) (Meyerhoff, 1999; Tan et al., 2011; Simarro et al., 2012; Smorenburg et al., 2000; Ben Salah et al., 2013; Yarchoan et al., 1986). Indeed, we use drug repositioning as the foundation for both a developmental framework for BSTs and a unified taxonomy against which BSTs can be characterised and stratified.

2. Repositioning

Thus far, no BST has been established through *de novo* discovery. Drug repositioning, on the other hand, can lead to BSTs that already assert a clinical history of application for different infection types. Drug repositioning is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication, and it has gained considerable momentum in the last decade: a third of drug approvals correspond to repositioning studies and such therapeutics generate 25% of the annual revenue for the pharmaceutical industry (Murteira et al., 2013; Naylor et al., 2015a). Public and non-profit organisations have released specific programmes to promote drug repositioning initiatives such as the Discovering New Therapeutic Uses for Existing Molecules initiative by the NIH National Center for Advancing Translational Sciences (Allison, 2012). Furthermore, a myriad of small repositioning-focused pharmaceutical companies have been created over the last two decades (Naylor et al., 2015b). Since new indications are built upon previous knowledge, such as pharmaceutical, manufacturing, and distribution data, both the drug development timeline and economic costs are substantially reduced (Dovrolis et al., 2017; Zhang et al., 2016; Brown and Patel, 2017; Zhou et al., 2020; Smith, 2011). Finally, repositioned candidates are already proven to be sufficiently safe in preclinical models and in early-stage trials, and are thus less likely to fail from a safety point of view in subsequent efficacy trials.

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Table 1
Examples of drugs repositioned to a new antimicrobial classification.

Therapeutic	Original class	Repositioned class	Approval year
Amphotericin B	Antifungal	Antiparasitic	1997 (Meyerhoff, 1999)
Doxycycline	Antibiotic	Antimalarial	Off-label (Tan et al., 2011)
Eflornithine	Antitumour	Antiparasitic	1990 (Simarro et al., 2012)
Miltefosine	Antitumour	Antiparasitic	2014 (Smorenburg et al., 2000)
Paromomycin	Antibiotic	Antiparasitic	1994 (Ben Salah et al., 2013)
Zidovudine	Anticancer	Antiviral	1987 (Yarchoan et al., 1986)

There are, however, several key limitations of drug repositioning. As drugs are approved after observing clear benefits within defined safety margins, the clinical utility of finding novel drug-target interactions is hindered by two key pharmacological factors: dosage measurements between new drug-target interactions and the ability to deliver the drug to particular targets at disease focal regions may vary relative to pre-established and approved dose ranges (Business Insights reports, 2011). As sufficient interactions must be made between the target and the drug (or its associated metabolites) within as minimal timeframe as possible, both factors encroach on the therapeutic's safety profile for the disease. Therefore, only at the clinical level can appropriate dosage levels and a working safety profile be established. If the novel potency falls outside of the established dosage range, phase I clinical trials must be initiated, effectively stripping drug repositioning's strategic advantage over *de novo* drug discovery. That being said, it is conceivable that a candidate can be repositioned through the implementation of delivery devices or reformulations to provide drug exposure to the targeted tissue whilst limiting exposure to other tissues (Datamonitor reports, 2012).

Next, there are notable intellectual property and economic challenges pertaining to drug repositioning (Sleigh and Barton, 2010). A minority of national legislations impede obtaining a patent for second or additional medical uses, though it is possible to protect a repositioned medical use in most major pharmaceutical markets. Moreover, many potential repositioning uses are either reported in PubChem or other online databases via publications (which range from peer-reviewed literature to blogs), or explored in clinical practice as off-label, non-registered uses (Verbaanderd et al., 2020). Though not endorsed by controlled clinical trials, the data is available publicly and affects therapeutic patentability. The European Union currently provides 8 years of data protection in addition to 2 years of market exclusivity; if a second indication is developed during the 8-year exclusivity period, an additional year of patent protection may be granted. The United States similarly grants an initial period of 5 years which may be expanded by 3 years for a new use (Breckenridge and Jacob, 2019). Finally, since drug repositioning is in itself a novel field in academia, one prevailing limitation is the lack of experts in the legal issues pertaining to it (Simsek et al., 2018).

This year saw drug repositioning emerging as the foremost treatment development strategy for the COVID-19 pandemic, which in turn has highlighted its importance as a general strategy for future global health emergencies. Repositioning studies that reclassify existing therapeutics as BSTs offer a pipeline of emergency-use therapeutics that can be readily accessed and reviewed during the onset of a future pandemic. Such a strategy obviates the need to search for repositioned candidates after the emergence of a pandemic and instead fosters the development of a class of treatments specifically in anticipation of infectious threats, thereby saving time in clinical trials, resources for vaccine development, and lives.

3. Reclassification

Reclassification is a simple method by which to consolidate successful repositioning studies. Due to the variability of repositioning studies, an evidence-based assessment is required in order to appropriately reclassify an antimicrobial as a BST. One such assessment has been propounded that distinguishes five drug repositioning evidence level (DREL) stages according to the amount and quality of evidence available (Table 2). The advantage of this particular system is its parallelism with classification schemes used for quantifying drug-drug interactions (Jansman et al., 2011). As quality of evidence increases from *in vitro* investigations to animal and human clinical trials, a higher DREL number is assigned accordingly. The DREL assessment was borne out of unsubstantiated claims for some repositioning projects and a lack of experimental evidence or corroboration with the literature (Oprea and Overington, 2015); such a scheme can simplify the evaluative process of repositioning studies and may succeed also in tempering heightened expectations for cures, particularly in the midst of a pandemic. A BST can thus be defined alternatively as a DREL 4 therapeutic for multiple diseases pertaining to more than one pathogen class.

As the prototypical BST, the antibiotic azithromycin provides a useful framework with which to understand how repositioning studies can lead to therapeutic reclassification (Firth and Prathapan, 2020). Clinical trials of azithromycin for malaria with or without other medications stretch as far back as 1998 (Andersen et al., 1998; Taylor et al., 2003), complementing a myriad of *in vitro* studies which confirm a lysosomotropic profile akin to that of the antimalarial chloroquine (Wilson et al., 2015; Tyteca et al., 2002). Indeed, according to the aforementioned repositioning classification system, azithromycin is a DREL 4 antimalarial. However, the lack of formal reclassification precluded its immediate consideration as a treatment for the current pandemic, and resulted instead in its unsuccessful combinatorial use with hydroxychloroquine, until the University of Oxford's RECOVERY trial initiated a large-scale, randomised azithromycin monotherapy arm several months later (Oliver and Hinks, 2020). In a pandemic, and indeed in general, multi-target agents are preferred over combination therapies due to more predictable pharmacokinetics, lower probabilities of drug interactions, and higher patient compliance. At the time of writing, several papers have now consolidated repositioning studies probing azithromycin's antiviral properties and over 80 corresponding randomised trials have been initiated (Sultana et al., 2020; Bleyzac et al., 2020). The azithromycin case study demonstrates that a lack of a formal reclassification system impedes the speed at which therapeutics are considered for pandemics, even in the face of decades' worth of repositioning studies. This raises an important corollary argument, that similar BSTs remain uncharacterised due either to a lack of repositioning studies or of consolidation of such studies.

Fortunately, characterisation of such BSTs is a self-perpetuating process; indeed, identification of azithromycin as a BST has spotlighted the broader antiviral pharmacology of macrolides, and similar successful studies of the broad-spectrum properties of nitazoxanide have permitted this therapeutic to be used as a scaffold for the design of *de novo* thiazolides (Fig. 1) (Rossignol and Cavier, 1976; Rossignol and Maisonneuve, 1984; Murphy and Friedmann, 1985; Dubreuil et al., 1996; Romero

Table 2
Drug repositioning evidence level (DREL) assessment of repositioning studies. BSTs are DREL 4 for diseases pertaining to two or more antimicrobial classes.

Drug repositioning evidence level	Quality of scientific evidence
0	No evidence; includes *in silico* predictions without confirmation
1	*In vitro* studies with limited value for predicting *in vivo*/ human situation
2	Animal studies with hypothetical relevance in humans
3	Incomplete studies in humans at the appropriate dose e.g. proof of concept; few cases from medical records; some clinical effects observed
4	Well-documented clinical end points observed for repositioned drug at doses within safety limits

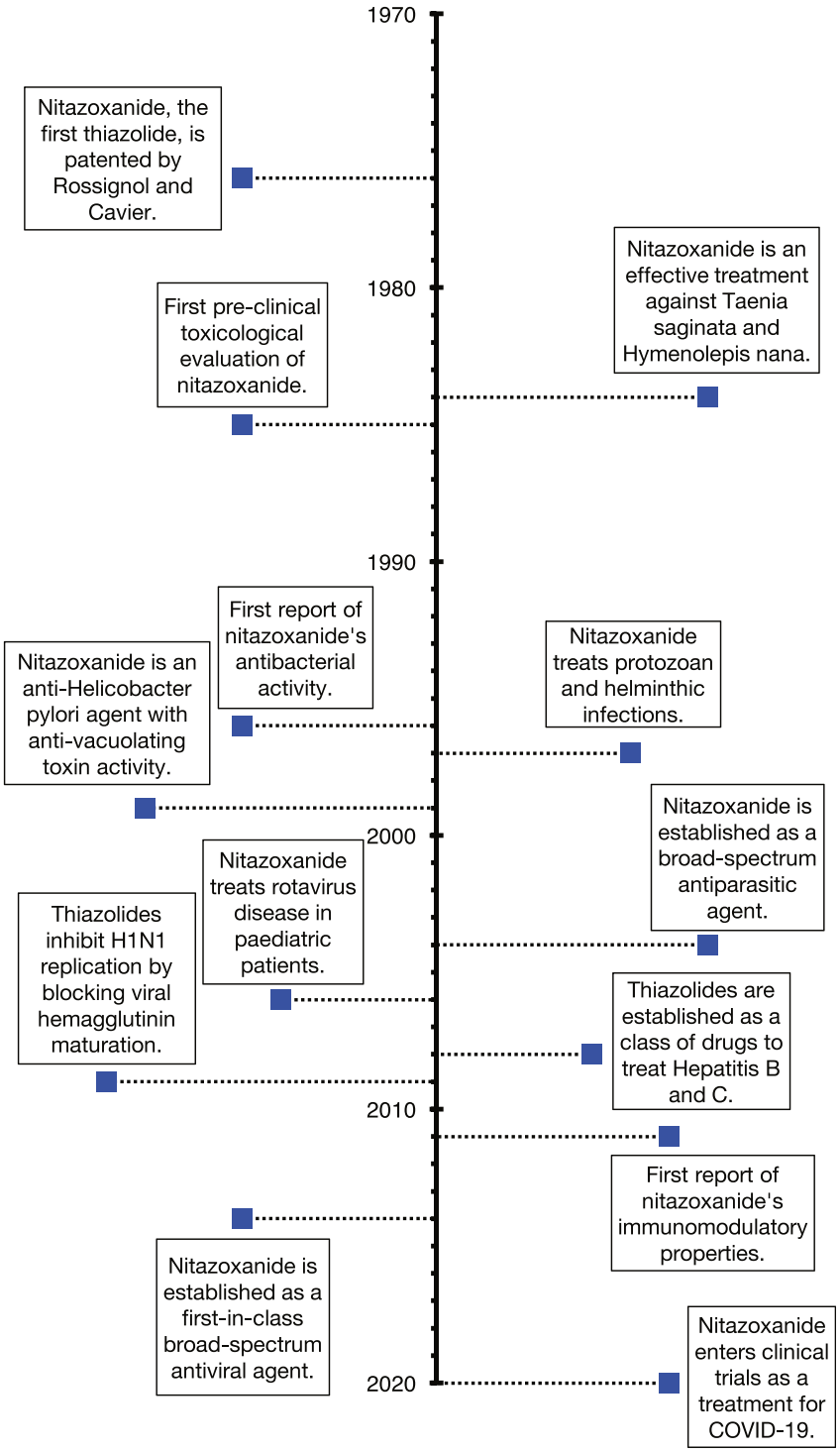

Fig. 1. Repositioning history of nitazoxanide.

Cabello et al., 1997; Yamamoto et al., 1999; White, 2004; Rossignol et al., 2006a, 2009a; Rossignol and Keeffe, 2008; Clerici et al., 2011; Rossignol and October 2014; Liu et al., 2020). BSTs such as azithromycin and nitazoxanide, due to a proven record of licensing and repositioning for a multitude of diseases, accordingly exhibit low cytotoxicity under both infectious and non-infectious conditions, thereby constituting potentially effective yet relatively safe emergency treatments for pandemics. A litmus test for the pharmacological effectiveness of BSTs is to evaluate their purported potency across various pandemics in history. With the clinical demonstration of its treatment of acute uncomplicated influenza almost a decade ago, nitazoxanide may have indeed proven an effective BST for the last century's Spanish Flu pandemic, highlighting the applicability of BSTs as a general emergency treatment class (Haffizulla et al., 2014).

In order to delineate a comprehensive clinical and pharmacological profile for a given therapeutic, repositioning studies must range from *in silico* and *in vitro* screening to large-scale, randomised clinical trials. It is thus important to note that pharmacological studies in particular are not limited to direct inhibition of pathogens but also encompass modulation of the host immunological profile with or without the presence of infectious agents. Host-targeted antiviral (HTA) properties, for example,

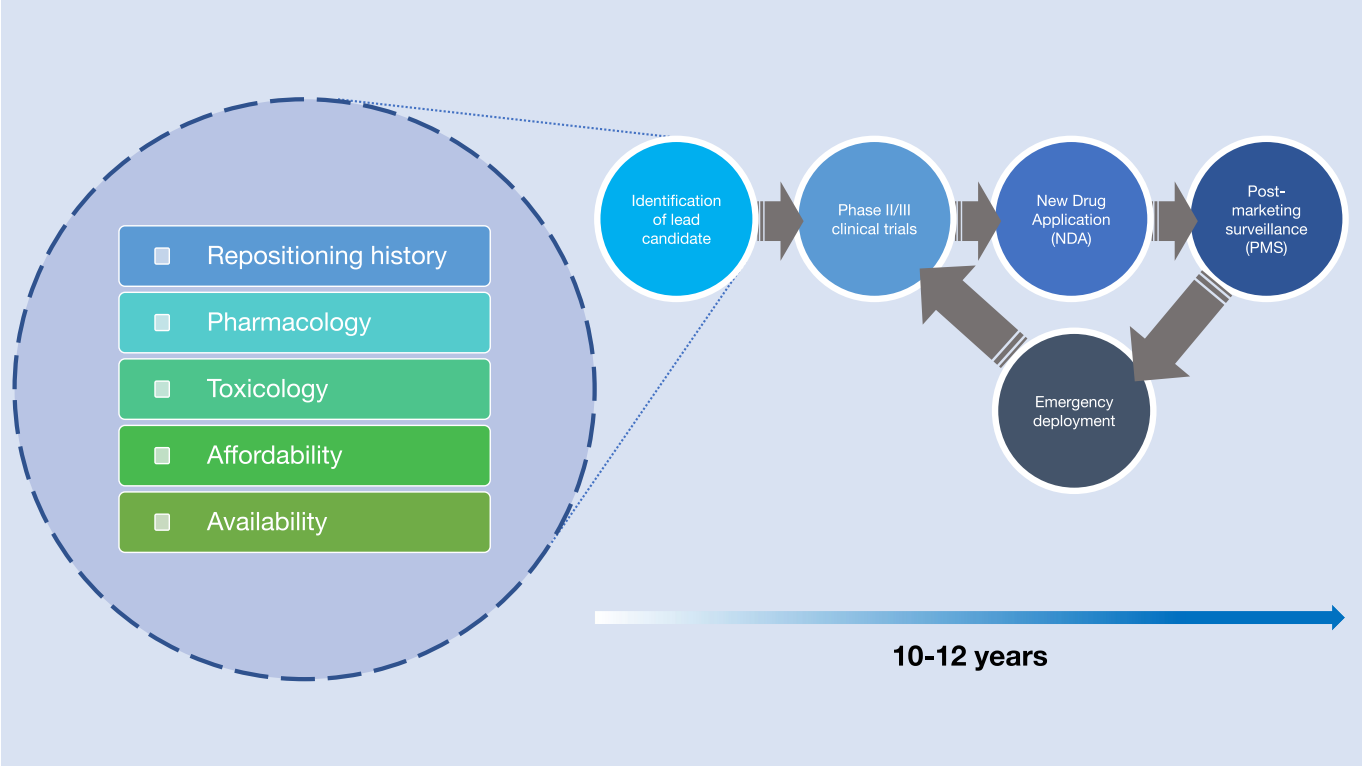

Fig. 2. Stages of broad-spectrum therapeutic (BST) development. Key parameters with which to evaluate emergency repositioned therapeutic candidates for pandemics are: A) Repositioning history. Candidates targeted for clinical studies can be prioritised according to their repositioning history and evidence (DREL); a longer history positively correlates with a safer and more widely used therapeutic and a large body of repositioning evidence is indicative of a broad-spectrum pharmacology (e.g. ivermectin and niclosamide). If an evaluation of a candidate's repositioning history reveals that it is DREL 4 for two or more antimicrobial classes, the candidate may directly enter PMS as a BST. B) Pharmacology. Evaluation of host-directed and pathogen-directed antimicrobial properties for both lead candidate and related compounds e.g. antiviral lysosomotropic properties of azithromycin and the wider macrolide class. C) Toxicological assessment, including the potential for antimicrobial resistance (AMR). Both pharmacological and toxicological information can be obtained from pre-existing *in silico*, *in vitro*, and preclinical studies of both the lead candidate and chemically similar compounds. D) Financial appraisal. Emergency therapeutics must be affordable by national healthcare systems in developing countries. E) Availability. Emergency therapeutics must be globally distributed to ensure sufficient deployment during a pandemic. Certain national legislations may impede obtaining a patent for further medical uses and can hinder candidate availability in certain regions. An ideal candidate would be included in the World Health Organization's List of Essential Medicines and available in all national healthcare systems. Both affordability and global availability may change after BST characterisation during post-marketing surveillance (PMS) and should be continually monitored. Overall, in addition to reduced cost and resources, drug repositioning usually takes 10–12 years compared to 15–20 for *de novo* drug development, which requires additional compound screening, preclinical studies, and phase I clinical trials. Successful deployment of BSTs for pandemics or bioterrorist attacks can iteratively refine and identify new use cases.

have been enumerated in macrolides in the form of inducing type I and type III interferon signalling, as is the case for azithromycin; and down-regulating ICAM-1, a major receptor for both *Haemophilus* and rhinovirus (RV) for clarithromycin (Firth and Prathapan, 2020). HTA properties of macrolides, which are primarily used as antibacterials, are a pharmacological idiosyncrasy gleaned from repositioning studies, and have already proven crucial to informing the repositioning of antibiotics for COVID-19. Interestingly, both azithromycin and nitazoxanide exhibit immunomodulatory properties, a prospective hallmark of BSTs. Thus, reclassification of therapeutics to BSTs and downstream application for future global health emergencies requires both a holistic understanding of their pharmacology in addition to their clinical effectiveness against the appropriate pathogen class.

Overall, reclassification to a BST is merely the final step to successfully reposition an antimicrobial against a new pathogen class. It is important to state, however, that this does not revise repositioning studies to a teleological practice for BST characterisation, but rather emphasises the importance of formally recognising when such studies reach a critical juncture towards reconceptualising an antimicrobial.

4. Regulation

Though currently only described in U.S. federal documents, BSTs have an important role in mitigating health threats on an international scale. As such, there is an incentive to globally regulate future BSTs, delineate guidelines for their use, and continually monitor potential adverse drug reactions (ADRs). The development of an international streamlined regulatory process as well as the establishment of a global pre-competitive knowledge transfer system for regulatory and scientific drug information have been among many ideas long proposed to overcome the 'valley of death' between academic classification of repositioned therapeutics and their clinical application; both are indeed essential for the regulation of emergency therapeutics (Oprea et al., 2011).

Post-marketing surveillance (PMS) is the practice of monitoring the safety of a therapeutic after it has been released on the market and is an imperative stage of pharmacovigilance (Huang et al., 2014). PMS can further refine, or confirm or deny, the safety of a given BST after it has been used in the general population by large numbers of people with a

wide variety of medical conditions (Vlahovic and Mentzer, 2011). A plethora of approaches is used to monitor drug and device safety, including spontaneous reporting databases, prescription event monitoring, electronic health records, patient registries, and record linkage between health databases (McNeil et al., 2010). These data are mined and reviewed to highlight potential safety concerns.

The monitoring of ADRs is an integral component of PMS. The World Health Organization (WHO) defines an ADR as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function' (Lindquist and Edwards, 2001). With regard to long-term use of drugs or the intake of drugs at wider timeframe intervals, follow-ups are crucial for the detection of ADRs. However, a limited number of participants undergo long-term trials, and ADRs have been observed in the order of 1 in 10,000 or fewer drug exposures (Hazell and Shakir, 2006). Ultimately, the shortcomings of premarketing trials and PMS throw into sharp relief the need to conduct investigative studies in perpetuity after a successful New Drug Application (NDA) and/or BST classification. Nevertheless, PMS practices have evolved significantly over the years, shifting from reactive approaches to risk prevention and improved communicative measures (Avery et al., 2011).

Due to their application for global health emergencies, BSTs are unique in their greater need for global regulation compared to other repositioned therapeutics. The WHO's Model List of Essential Medicines contains the drugs considered to be the safest and most effective to meet the most important needs of a health system. It is frequently used to develop healthcare infrastructures and has been a template adopted by over 150 nations (Persaud et al., 2019). Inclusion of a list of emergency treatments to be deployed in the event of a pandemic or global bioterrorist attack would ensure that national health systems around the world are appropriately primed for infectious threats, needing only to await clearance from the WHO before BST administration. In the interest of adequately supplying health systems around the world with emergency treatments, the WHO should also monitor both the global distribution and cost of BSTs: two factors which have proven decisive for the therapeutic candidates in the current pandemic (Ledford, 2020).

Finally, many BSTs are subject to the age-old limitation of antimicrobial resistance (AMR) and, in the context of a global health emergency, must be used within a short-term time frame until a vaccine or long-term treatment solution is found (Antimicrobial resistance, 2020). Antibiotic overuse has been a major concern during the course of the current pandemic and the prospect of AMR strengthens the mandate for global oversight in order to prevent overuse or misuse of BSTs (Sirijatuphat et al., 2018). Different global agencies such as the Global Antimicrobial Resistance Surveillance System under the WHO, Global Health Security Agenda (GHSA), and the Antimicrobial Resistance Action Package have made significant efforts to tackle AMR on an international scale (Belay et al., 2017). Ultimately, regulation of BSTs follows from the regulation of repositioned therapeutics but must include additional surveillance on an international scale.

5. Discussion

The potential of BSTs is yet to be realised. As the discovery of antibiotics has advanced our understanding of bacterial infection, so the discovery of BSTs may unearth infection mechanisms conserved across pathogen classes. Certainly, identification of cellular and nuclear signalling pathways targeted by BSTs, such as azithromycin's modulation of antiviral responses via IFNβ activation and nitazoxanide's inhibition of autophagy via ING1 upregulation, will instigate and iteratively improve BST drug-disease interaction networks, further contributing to a shift away from the 'single drug-single target' paradigm and towards a polypharmacological one in which therapeutics engage multiple targets within the interactome. With an increasing number of repositioning studies conducted worldwide, particularly with the onset of the COVID-19 pandemic, it is foreseeable that new BSTs will be identified. Classifying BSTs against different pathogenic classes requires a unified taxonomy, which may be derived from the DREL system: four antimicrobial types (antibiotics, antifungals, antiparasitics, and antivirals) can yield four DREL numbers. Thus, a BST that is used clinically as an antimalarial and an antiviral but has not been studied as an antibiotic or antifungal is a 0:0:4:4 BST; the order of the DREL numbers here are: antibiotic = 0, antifungal = 0, antiparasitic = 4, antiviral = 4. According to this system, azithromycin is a 4:0:4:2 BST and nitazoxanide a 4:0:4:4 BST. With an accumulating arsenal of BSTs, a concomitant taxonomic structure can direct future repositioning studies, facilitate comparative therapeutic investigations, and inform clinical and emergency treatment application.

The herein discussed BST developmental framework via drug repositioning is derived from the therapeutic development strategy for the current pandemic, and is accompanied by a series of benefits and limitations; its affordability, efficiency, and safety are palliated by prevailing legal limitations and the growing risk of AMR, and henceforward there remains a considerable need to globally regulate BSTs with respect to their IP, PMS, availability, and administration (Fig. 2). Overcoming such limitations, however, will herald a significant step towards bridging the antiquated gap between academic classification of therapeutics and their downstream clinical application.

6. Conclusion

The pandemic has challenged our perception of therapeutics. No longer do they asseverate static, well-defined pharmacological profiles for commensurate diseases, but rather harbour interminable repositioning potential that is realised only through *in silico/in vitro* screening, clinical investigation, and now: reclassification. The inauguration of the BST as a formal antimicrobial class is both a milestone and a symbol for the growing acknowledgement of antibiotics, antifungals, antivirals, and antiparasitics that exhibit clinically effective pharmacological activity against pathogen types tangential to their original classification. In the future, an increasing armamentarium of BSTs will enable the identification of conserved chemical and pharmacological properties, which in turn will facilitate the longer-term development of a pipeline for *de novo* BSTs, as first envisioned by the U.S. Strategic Plan for Biodefense Research. As stated therein, the development of broad-spectrum therapeutics, tempered by the desiderata of antimicrobial stewardship and administrative oversight, 'will provide enormous benefits to biomedical research and usher in 21st century medicine for future generations'.

Credit author statement

All authors contributed equally to the work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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