Is repositioning of drugs a viable alternative in the treatment of tuberculosis?

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Antimicrobial resistance is a serious problem because of the scarcity of new antibiotics effective against pathogens such as methicillin-resistant Staphylococcus aureus, β-lactamase-producing Gram-negative bacteria and multidrug-resistant Mycobacterium tuberculosis. Extensively drug resistance is particularly worrying in tuberculosis (TB), since the causative bacteria have become resistant to almost all available first- and second-line drugs and resistance is a threat to achieving control of the disease. Development of new drugs is a lengthy and costly endeavour. This is a particular problem for antibiotics, usage of which is likely to be of limited duration, and is even more true of antibiotics whose use is restricted to the treatment of a disease, such as TB, that is considered to be ‘poverty related’, and for which the return on the investment is seen as non-attractive. In spite of this, there is an emerging pipeline of new drugs under development that hopefully will bring new anti-TB drugs to the market in the near future. The strategy of drug repurposing, finding new uses for existing approved medicines, has seen unexpected success in other medical areas. More than one blockbuster drug has originated from this strategy. And in the field of TB, there have been several examples in recent years of this approach leading to the use of drugs for which there is undeniable evidence of efficacy in the treatment of the disease, the best example being the fluoroquinolones, which were not developed originally to treat TB. This article reviews some examples of repurposing of drugs in the treatment of TB, newer candidates for repurposing for which there is already preliminary evidence of activity and possible new options that merit further investigation.

Keywords: Mycobacterium tuberculosis, antimicrobials, repurposing, drug resistance

Introduction

Tuberculosis (TB) remains an important public health problem worldwide. With 9.4 million estimated cases and 1.7 million deaths attributed to the disease in 2009, it is one of the major killers among infectious diseases.1 The HIV/AIDS pandemic and the emergence of drug resistance are considered to be the two major reasons for the deterioration of the TB situation around the world, especially in less-developed countries.2,3 Treatment options for infection with drug-resistant strains of Mycobacterium tuberculosis are particularly limited.4 After the description of multidrug-resistant (MDR)-TB, extensively drug-resistant (XDR)-TB followed and, more recently, so-called totally drug-resistant (TDR)-TB.5–8 MDR-TB is defined as TB resistant to at least rifampicin and isoniazid, two key drugs in the treatment of TB. XDR-TB is defined as disease caused by bacteria that, in addition to being MDR, are resistant to any fluoroquinolone and to any of the three injectable second-line drugs capreomycin, kanamycin or amikacin. A formal definition of TDR-TB is not yet available, and some researchers have proposed the term ‘XXDR’ for extremely drug resistant, that is mostly resistant to all available first- and second-line anti-TB drugs.9

The emergence of drug resistance is not exclusive to M. tuberculosis. The last decade has seen a continuous increase in antimicrobial resistance among several other bacterial pathogens and microorganisms such as Staphylococcus aureus, Streptococcus pneumoniae, the Enterobacteriaceae, non-fermenters such as Pseudomonas aeruginosa and parasites such as Plasmodium falciparum.10–12 This situation highlights the need for the continuous development of new and effective antimicrobials, ideally with new mechanisms of action, that would help to counter the development of drug resistance by the different pathogens.

There is a common belief that pharmaceutical companies in general are not very interested in developing or in researching new antimicrobials. One possible reason for this is the lack of big markets, which would translate into less profit compared with drugs developed for other more chronic ailments.13,14 In fact, in the last 25 years very few new antimicrobials have been introduced or approved for clinical use.15 In most cases the efforts invested in developing new antimicrobials have been driven by the emergence of drug resistance in pathogens that were initially susceptible to many antibiotics or specific agents, a good example of this being the spread of methicillin-resistant S. aureus (MRSA).16
Very few completely new agents have been developed in recent years. In many instances, development has been attained by modification of existing scaffolds or modifications of existing molecules, as has been done for cephalosporins, tetracyclines and oxazolidinones. This is also the case in TB, for which only two or three modified or new antibiotics are currently undergoing clinical evaluation.

In view of this, the concept of repurposing or repositioning of drugs is gaining much attention. A simple definition of this is to investigate new uses for existing approved drugs. There are several examples in the medical literature and recent therapeutic history that support this concept. Among the most publicized cases are those of minoxidil (initially developed as a treatment for hypertension but subsequently used to treat hair loss), sildenafil (successfully repurposed from a treatment for hypertension to one prescribed for erectile dysfunction) and thalidomide (repositioned from a sedative, analgesic and antiemetic and now used successfully in the treatment of erythema nodosum leprosum and multiple myeloma). In the case of TB, a good example of repurposing of drugs already exists in the form of fluoroquinolones, which were originally introduced for the treatment of other infections and are now being used as second-line drugs for MDR-TB. In this article, we review some examples of drugs repurposed for the treatment of TB, newer candidates for repurposing for which there is already preliminary evidence showing activity and possible new options that merit further investigation.

The fluoroquinolones: a success story?

The first quinolone to be described was nalidixic acid, which was discovered as a by-product during the purification of the antimalarial drug chloroquine in 1962. Nalidixic acid had a very narrow spectrum of activity and was mainly used to treat urinary tract infections. All fluoroquinolones currently in use are synthetic derivatives of the parent compound nalidixic acid with changes at position 1, 6, 7 or 8 of the chemical structure, yielding much more potent and broad-spectrum antibiotics. The mechanism of action of quinolones is inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV, two enzymes essential for bacterial viability. Quinolone resistance develops mainly by chromosomal mutations in genes coding for the A and B subunits of the target proteins GyrA, GyrB, ParC and ParE. Resistance can also occur by reduced uptake of the drug or by an increased efflux mechanism, which may be plasmid mediated.

In *M. tuberculosis*, only type II topoisomerase (DNA gyrase) is present and, thus, this enzyme is the only known target for fluoroquinolone activity. DNA gyrase is a tetramer composed of two A and two B subunits, encoded by the genes gyrA and gyrB, respectively, which catalyse the supercoiling of DNA. The first reports on the in vitro activity of fluoroquinolones against *M. tuberculosis* and other mycobacteria appeared a long time ago. Soon after, a first report on the use of ofloxacin in the treatment of a small group of patients with pulmonary TB showed that there was a reduction in the bacillary load in the sputum and there was a conversion in 5/19 patients treated with 300 mg daily for 6–8 months. Following this initial report several studies confirmed the antimycobacterial activity of quinolones, mainly ciprofloxacin and ofloxacin, in vitro, in experimental animal models and in the preliminary treatment of TB patients. However, resistance to ciprofloxacin soon emerged when it was used to treat patients with MDR-TB. Since then, more potent and active third- and fourth-generation fluoroquinolones have been synthesized showing a broad spectrum of activity against several microorganisms, both Gram-positive and Gram-negative.

Two of these newer fluoroquinolones, moxifloxacin and gatifloxacin, are currently being investigated in on-going clinical trials to assess their efficacy as first-line anti-TB drugs based on promising preliminary clinical evaluations. In addition, a recent meta-analysis has shown that later-generation fluoroquinolones are useful for the treatment of XDR-TB in spite of susceptibility testing showing resistance to representative fluoroquinolones, such as ofloxacin or ciprofloxacin. Although no results of Phase III clinical trials are available yet, it is expected that, if successful, fluoroquinolones could contribute to shortening the current duration of treatment for drug-susceptible TB.

Do we have a success story then, with the repositioning of fluoroquinolones for the treatment of TB? It is difficult to answer that question at present. It will depend in part on the results of on-going Phase III clinical trials, but also on whether we are able to control or limit the development of resistance to these newer fluoroquinolones. As Takiff and Guerrero argue in a recent article, caution must be exercised, since the recent history of the use of antibiotics shows that resistance can rapidly emerge if the antibiotic is not used properly or if it is given as monotherapy. Fluoroquinolones have been no exception to this, as is shown by reports of resistance occurring after only short periods of exposure to the drug as monotherapy for other bacterial infections, although other studies have not seen this effect. Probably it will depend on us on how well the newer fluoroquinolones are used and if they are given only when strictly necessary to avoid the development of resistance and to preserve their usefulness in the treatment of TB as a repositioned drug.

The case of linezolid

Linezolid is a synthetic drug belonging to the oxazolidinone class of antibiotics and was the first synthetic drug of this class to be approved for clinical use, in 2000. It was originally introduced to treat nosocomial pneumonia and skin infections due to Gram-positive bacteria. It is well suited for the treatment of severe infections caused by MRSA and vancomycin-resistant enterococci (VRE). However, it is not recommended for Gram-negative bacteria owing to their intrinsic resistance mediated by efflux pumps. Its discovery was a result of medicinal chemistry and serendipity when DuPont laboratories, as part of a screening programme, found high antibacterial activity in compounds derived from the oxazolidinone parent molecule. Development was discontinued because of their toxicity, but Upjohn laboratories at a later time continued their development, producing two non-toxic derivatives: linezolid and eperezolid. The mechanism of action of linezolid is inhibition of protein synthesis through its binding to the P site of the 50S ribosomal subunit. Mutations in the 23S rRNA allowed identification of the peptidyl transfer centre as the exact site of action of the drug. Since then, and after many clinical evaluations, linezolid has become established as a well-known treatment for several Gram-positive...
bacterial infections, and in some cases is the only available and effective treatment option, as is the case in some community-acquired S. pneumoniae pneumonia.53

The first report of the activity of linezolid against M. tuberculosis appeared in 1991. Ashktekar et al.54 tested linezolid in vitro and in vivo in a mouse model of infection and found it to be active against M. tuberculosis and other mycobacteria with MICs of 1.5–4.0 mg/L. Subsequent studies confirmed the good activity of linezolid against M. tuberculosis both in vitro and in infected mice.55–57 Further studies also showed that linezolid was synergic with rifampicin in drug-susceptible strains and that it had great capacity for restricting the selection of resistant mutants, as defined by a mutant prevention concentration of only 1.2 mg/L.58,59 Based on these studies, linezolid was first used in a limited number of TB patients to assess its efficacy and tolerability during long-term administration.60,61 These studies showed that, although linezolid was effective in treating patients with MDR-TB, its prolonged use was associated with toxicity causing anaemia and peripheral neuropathy that persisted after administration of a half-dose of 600 mg once daily.61 These adverse effects after long-term administration were also reported in a systematic review of the available evidence, which found that almost 50% of patients receiving linezolid as part of combination therapy for mycobacterial infections, mainly TB, developed neuropathies or anaemia.62 To complicate matters further, the first report of linezolid-resistant clinical isolates soon appeared. These resistant isolates lacked mutations in the potential target genes and no conclusion on the possible mechanism of resistance was drawn.63 The influence of efflux pumps has been more recently identified as a factor contributing to the resistance of M. tuberculosis to the drug.64 In spite of these difficulties, linezolid is being used in selected cases of drug-resistant TB and when fewer treatment options are available, as in the case of XDR-TB patients.65,66

What is the future for linezolid in the treatment of TB? The advantages of linezolid are undeniable, oral administration with high bioavailability, very good penetration and distribution into tissues and excellent pharmacodynamic parameters. But along with this comes the problem of adverse effects during long-term administration, as is the case in the treatment of TB. This remains the main problem preventing successful repositioning of this drug and limits its current application to special circumstances, such as severe cases of drug resistance. A recent study found that administering a dose of 300 mg of linezolid daily was effective in treating MDR/XDR-TB and was probably associated with fewer side effects.67 The good news is that, based on this successful experience, pharmaceutical companies are now interested in research on oxazolidinones and there is already an analogue of linezolid, PNU-100480, which has excellent activity against M. tuberculosis in mice.68 The current evidence shows that PNU-100480 is not associated with the adverse effects shown by linezolid when tested in healthy volunteers.69 PNU-100480 has recently completed a Phase I clinical trial.

Activity of trimethoprim/sulfamethoxazole against TB

Although resistance of M. tuberculosis to the combination trimethoprim/sulfamethoxazole has been taken for granted, the first evidence of activity of sulfonamides in the treatment of TB dates back several decades.70 Owing to modest activity and some toxicity problems at the time, and after the introduction of more potent drugs such as isoniazid and streptomycin, the use of sulfonamides was abandoned for the treatment of TB. A revival of interest in the possible use of trimethoprim/ sulfamethoxazole in TB was spurred by a recent report by Forgacs et al.71 of an immunocompromised patient who apparently responded to the drug combination based on clinical defer-vescence and without administration of any other antibiotic. Based on this finding, the authors tested 44 clinical isolates of M. tuberculosis, including four MDR isolates, and found 43/44 to be susceptible to the drug combination, using susceptibility criteria available for Mycobacterium kansasii and Mycobacterium marinum, in the absence of standardized guidelines for testing trimethoprim/sulfamethoxazole with M. tuberculosis.71,72 A combination of a sulfonamide and folate antagonist has been used effectively for treating non-tuberculous mycobacterial infections.

Stimulated by this observation, two other recent studies have addressed this issue by testing the activity of sulfamethoxazole, trimethoprim or the combination of both against clinical isolates of M. tuberculosis. Ong et al.73 assuming that the sulfon component of the combination was responsible for the anti-TB activity reported previously, evaluated the activity of sulfamethoxazole alone against 12 consecutive M. tuberculosis isolates obtained from patients (nine pulmonary and three extrapulmonary samples) all susceptible to the first-line drugs. All isolates were susceptible to sulfamethoxazole, with an MIC ≤ 38 mg/L, within the range of achievable serum concentrations. More recently, a second study evaluated the susceptibility of 117 drug-susceptible and drug-resistant isolates of M. tuberculosis to sulfamethoxazole, trimethoprim and the combination trimethoprim/ sulfamethoxazole.75 Sulfamethoxazole inhibited 80% and 99% of growth in all isolates at 9.5 and 38 mg/L, respectively, independently of the isolates' susceptibility to the first-line drugs. Moreover, there were no changes in the MIC50 or MIC90 throughout a 12 year period. Trimethoprim alone had no effect at >8 mg/L and the combination at a 1:19 ratio lacked any synergistic or additive effect.75

The mode of action of trimethoprim/sulfamethoxazole is inhibition of bacterial synthesis of tetrahydrofolic acid, the active form of folic acid, vital for bacterial function. Sulfamethoxazole, being a structural analogue of para-aminobenzoic acid, inhibits the synthesis of dihydrofolic acid, while trimethoprim, a structural analogue of the pteridine moiety of dihydrofolic acid, competitively inhibits dihydrofolate reductase (DfrA), and the production of tetrahydrofolic acid from dihydrofolic acid.76 This might explain why trimethoprim by itself was inactive, since it has been shown that, in M. tuberculosis, DfrA is not completely essential and that disruption of the dfrA gene did not prevent infection in mice.77 It was also recently suggested that mutations in dfrA play a role in resistance to isoniazid,78 although other, more recent, studies have not corroborated this assertion.79,80 Furthermore, mutations in thyA, which encodes thymidylate synthase, have been also suggested to confer resistance to trimethoprim/sulfamethoxazole.81

Taking all this into consideration, and to better define the possible role of trimethoprim/sulfamethoxazole as a repositioned drug, adding to the anti-TB drug armamentarium, it will be
necessary to further corroborate the few available studies that have reported activity of trimethoprim/sulfamethoxazole, or perhaps sulfamethoxazole alone, against a larger number of clinical isolates from different settings. It would also be interesting to investigate in more detail the possible cross-resistance between trimethoprim/sulfamethoxazole and para-aminosalicylic acid or isoniazid, or even ethionamide. It would also be desirable to correlate all this with the investigation of possible mutations in the $dfrA$ and thy$A$ genes. This is particularly important in view of the WHO recommendation for the wide implementation of trimethoprim/sulfamethoxazole prophylaxis in people living with HIV.82

The silent repositioning of clofazimine

Clofazimine is a lipophilic rimenophenazine compound originally described in 1957 as having ‘anti-TB’ activity.83 It has become established since the early 1960s as an anti-leprosy agent and is now part of the standard multidrug therapy for leprosy recommended by WHO.84 Based on some limited studies, and owing to the scarcity of treatment options when dealing with severe cases of drug-resistant TB, clofazimine is now in the WHO list of second-line group 5 drugs for the treatment of MDR-TB.85

The precise mode of action of clofazimine has not been completely elucidated. Some recent studies, however, have shed some light on this, pointing to the bacterial outer membrane as the possible site of action of the drug.86

A renewed interest in clofazimine for the treatment of drug-resistant TB has been stimulated by a recent report of its effective application in a short regimen to treat a cohort of drug-resistant TB patients.87 The authors describe a 9 month regimen that contained clofazimine together with kanamycin, gatifloxacin, ethambutol, isoniazid, pyrazinamide and prothionamide in the intensive phase, achieving a cure rate of 87.9% with only two cases of recurrent disease. At an estimated cost 225 euros, the regimen was well tolerated, and only 5.8% of patients defaulted.87 Other recent studies, however, do not report such impressive results.88 On the other hand, in a murine model of infection, inclusion of clofazimine in combination with TMC207, PA-824 and PNU-100480 was superior to a first-line regimen containing rifampicin, pyrazinamide and isoniazid.89

Notwithstanding the very good in vitro activity of clofazimine against $M$. tuberculosis and remarkable results as part of seven drug combination therapy in a group of MDR-TB patients, it retains some undesirable effects that might not be acceptable in certain populations, especially when it has to be administered for extended periods of time. At present it represents a good reserve drug to be used in cases where few other options are available.

The return of $\beta$-lactam antibiotics

$\beta$-Lactam antibiotics have in general been considered ineffective against $M$. tuberculosis. This has been mainly attributed to the low permeability of the cell wall and the presence of an extended-spectrum $\beta$-lactamase.90 Additional studies, however, have shown that, in the presence of a $\beta$-lactamase inhibitor, $M$. tuberculosis can transport cephalosporins and penicillins through the cell wall at similar rates as $P$. aeruginosa, which is normally susceptible to $\beta$-lactam antibiotics.91 The mode of action of $\beta$-lactam antibiotics is inhibition of bacterial $\beta$-$\beta$-transpeptidases involved in the biosynthesis of the cell wall. It has been shown that in $M$. tuberculosis the peptidoglycan contains up to 80% 3–3 cross-links formed by a new $\beta$-$\beta$-transpeptidase that is the likely target of carbapenems.92 $M$. tuberculosis has one highly active class A $\beta$-lactamase, BlaC, encoded by the bla$C$ gene, which in knockout experiments was shown to render the bacteria more susceptible to the action of $\beta$-lactam antibiotics.93 It has also been shown that, in spite of having a broad substrate specificity, BlaC was irreversibly inhibited by clavulanic acid, a $\beta$-lactamase inhibitor used in the treatment of other bacterial infections.94 Adding to this, the same group of researchers demonstrated that meropenem, which is a potent member of the carbapenem family, was a poor substrate for BlaC and that, additionally, it has the ability to act as an inhibitor of BlaC.95 Moreover, the combination meropenem/clavulanate had potent activity against laboratory strains of $M$. tuberculosis with MICs below 1 mg/l, was equally effective against aerobically and anaerobically grown cultures and inhibited the growth of a small number of XDR-TB strains.95

With this evidence available, other researchers have started to evaluate the effectiveness of $\beta$-lactam antibiotics, especially carbapenems, against $M$. tuberculosis and to treat a limited number of patients with drug-resistant TB. Chambers et al.96 evaluated the effectiveness of imipenem for the treatment of TB in a mouse model and in patients with MDR-TB. Although imipenem was found to be less effective than isoniazid, it significantly reduced the numbers of bacilli in the lungs and spleens and improved survival in mice, while it also cleared cultures in 8/10 patients who received imipenem in combination with other first- or second-line drugs.96 Similar results were obtained in a more recent study in which imipenem, meropenem and ertapenem were tested alone or in combination with clavulanate in a mouse model of TB. The MICs of the three drugs in the presence of clavulanate were reduced 4–16-fold, and in the mouse model the combination of imipenem or meropenem with clavulanate significantly increased the survival of the mice but did not prevent bacterial growth in the lungs.97 More recently England et al.98 also evaluated combinations of carbapenem/clavulanate both in $M$. tuberculosis-infected 1774A1 murine macrophages and in C57Bl/6 mice using the reference strain H37Rv. They found a 1.5–2.0 log reduction of bacterial burden in the macrophages after 6 days of treatment, especially with imipenem and meropenem, comparable to the findings in the isoniazid- and rifampicin-treated controls. In mice, meropenem alone or in combination with clavulanate produced a significant reduction in bacterial load in both lungs and spleens after 2 weeks of treatment and further modest reduction at 4 weeks. In this study, the addition of clavulanate did not significantly increase the killing in lungs or spleens at those timepoints.99 Finally, a recent report presents the results of treatment of six patients with bilateral pulmonary XDR-TB who received a salvage regimen containing meropenem/clavulanate plus the remaining active second-line drugs and pyrazinamide and cycloserine. Culture conversion was obtained in all but one patient after 8–20 weeks of treatment and no relapses occurred after 8–25 months of follow-up.99

What all these studies show is that, among carbapenems, meropenem in combination with clavulanate is very active in
vitro against *M. tuberculosis* grown either aerobically or anaerobically, and is also active inside macrophages and effective in mice infected with *M. tuberculosis*. The limited data available in humans have also shown promising results in combination therapy against severe cases of drug-resistant TB, for which not many other effective drugs remain available. Both meropenem and clavulanate are FDA-approved drugs and lack important side effects. One disadvantage is that they need to be given via parenteral administration.

**Unusual suspects**

In addition to the well-known examples of candidates for repurposing mentioned above, there are other examples worthy of attention that have been reported. The case of mefloquine is one of them. Mefloquine is a quinoline derivative long used for the prophylaxis and treatment of chloroquine-resistant malaria. Several years ago as a result of a wide screening programme, mefloquine was found to be active *in vitro* and *in vivo* against *Mycobacterium avium*. Other later studies found it also to be quite active *in vitro* against *M. tuberculosis*. This should come as no surprise, since TMC207, a diarylquinoline, is an active antimycobacterial drug currently in clinical trial as anti-TB drug. Being also a quinoline derivative, there is a striking similarity between the two molecules, and the mode of action of TMC207, which specifically inhibits mycobacterial ATP synthase, with mutations in the *atpE* gene in resistant mutants, is not that different from the suggested target of mefloquine in *S. pneumoniae*, the F$_0$F$_1$ bifunctional ATP synthase/ATPase.

Mefloquine, however, is not exempt from important side effects, the most important being at the neurological level, and there are no current reports of its use in the treatment of TB patients. Spurred by these findings, it has been reported that a number of new mefloquine derivatives have already shown important activity against *M. tuberculosis*, and this will hopefully lead to modified compounds that lack the toxicity of the parent mefloquine compound but retain its antimycobacterial activity.

Phenothiazines originally developed as antipsychotic drugs are a similar case. These compounds exert their action at the level of the plasma membrane in eukaryotic cells, and it was hypothesized that they might have a similar effect in the plasma membrane of bacterial cells. Not much later this proved to be the case when it was shown that both MRSA and MDR *M. tuberculosis* could be killed by thioridazine, a member of the phenothiazines, at concentrations below those normally attained in patients receiving this drug. Thioridazine has also been shown to be active against intracellular MDR *M. tuberculosis* and in a murine model of TB infection. There is now limited evidence that its use in combination therapy for extreme cases of drug-resistant TB might be useful and, in some cases, life-saving for the affected patients. The main caveat here is that thioridazine is known to cause cardiac side effects, specifically prolongation of the QT interval, although these effects were not observed in the reported study, in which the patients receiving the combined therapy were under strict medical control. Table 1 shows an overview of the main drugs proposed as repurposed antibiotics to treat TB.

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<td>Linezolid</td>
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**Future perspectives**

It is well known that development of a new drug takes a lot of time and needs a lot of money. Current estimates indicate US$800 million to US$1 billion and 10–17 years from the point of development to reaching the market. It has also been argued that the number of approved drugs relative to the investment has declined in recent decades. Two culprits are mentioned as the reason for this decline: the rational drug design strategy directed against specific biological targets and the failure to investigate additional effects that the drug under development might have. When it comes to antimicrobials the
problem is even worse since it is widely considered that searching for new antibacterials is particularly high risk. Additionally, in most cases development of antibacterial drugs has been driven by the emergence of highly resistant pathogens.18

In TB the situation is similar, being a disease considered to ‘poverty related’; in consequence, the expectations of the industry of a sizeable market are low. Notwithstanding the existence of an emerging drug pipeline for TB,119 the approach of finding new uses for existing and already approved drugs might not be a bad idea. Of the drugs and examples reviewed in this article, it is apparent that fluoroquinolones at least have been almost successfully repositioned, being now considered almost as standard of care for TB treatment. Oxazolidinones may follow soon if the on-going studies confirm the previous findings not only with linezolid, but also with the newer formulations such as PNU-100480, which lacks the common side effects of the former. Considering their wide availability and relatively safe use, an attractive option for repurposing in TB seems to be the β-lactam antibiotics, especially a carbapenem, in combination with a β-lactamase inhibitor. The recent results of their experimental use are very encouraging. Alternative formulations, however, would be necessary to avoid the need for parenteral administration. We should not shy away from looking for alternative treatment options among already approved drugs. The case of thioridazine is probably a good example. This antipsychotic, developed many years ago, has shown undeniable activity in vitro, ex vivo and in vivo against M. tuberculosis. Moreover, it has been successfully used in a limited number of patients with severe forms of drug resistance, with very good results. If we follow the available published evidence, it would be reasonable to consider seriously starting larger trials to assess its effectiveness in the treatment of drug-resistant TB. Nevertheless, recommendations on the use of these repurposed drugs must follow strict criteria and careful administration to avoid the risk of a rapid development of drug resistance. We all know that, in the end, it remains a constant combat between us and the pathogen.

Transparency declarations
None to declare.

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