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OPINION

Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void?

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Abstract | Concern over antibiotic resistance is growing, and new classes of antibiotics, particularly against Gram-negative bacteria, are needed. However, even if the scientific hurdles can be overcome, it could take decades for sufficient numbers of such antibiotics to become available. As an interim solution, antibiotic resistance could be 'broken' by co-administering appropriate non-antibiotic drugs with failing antibiotics. Several marketed drugs that do not currently have antibacterial indications can either directly kill bacteria, reduce the antibiotic minimum inhibitory concentration when used in combination with existing antibiotics and/or modulate host defence through effects on host innate immunity, in particular by altering inflammation and autophagy. This article discusses how such 'antibiotic resistance breakers' could contribute to reducing the antibiotic resistance problem, and analyses a priority list of candidates for further investigation.

Resistance to current antibiotics is rapidly increasing. In its 2014 report of global antimicrobial resistance, the World Health Organization (WHO) portrayed high levels of antibiotic resistance in the bacteria that cause common infections. A number of leading authorities have issued passionate statements urging action, including the Director-General of the WHO, Margaret Chan; the Director of the Wellcome Trust, Jeremy Farrar; and the Director of the US Center for Disease Control (CDC), Tom Frieden. The United Kingdom's Chief Medical Officer, Sally Davies, warned that the country could find itself back in the nineteenth century in terms of its ability to treat bacterial infections. The seriousness of the threat has been compared with those of global warming and terrorism (see Further information).

The so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) are especially important owing to their role in many infections in human organs (such as the lung and urinary tract), the frequency of antibiotic resistance amongst them and the lack of alternative antibiotics[1]. Several of these pathogens are Gram-negative bacteria, which are of particular concern as in these organisms resistance of up to 50% against carbapenems, the current last line of defence, has been reported in some developing countries[1]. A few new antibiotics against Gram-positive bacteria have become available in recent years, but no totally new class of antibiotic has been introduced for the treatment of Gram-negative infections for more than 40 years.

In South Asia, the Middle East and the Mediterranean, modern medicine is already under threat from these multidrug resistant (MDR) Gram-negative bacteria[2] (*K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp.). European data spanning 2005–2010 indicate growing resistance to cephalosporins, fluoroquinolones and aminoglycosides, and a 30% mortality rate for patients with septicaemia due to MDR *Escherichia coli*[3]. Data from the USA show a similar pattern. The 2013 report from the CDC highlighted carbapenem-resistant Enterobacteriaceae (CREs) as an urgent threat[4]. In Asia, substantial resistance has emerged in both India and China, with resistance levels reported in the range of 50–80%. This has caused increased use of carbapenems, which were previously reserved for extreme cases of infection in the very sick, the immune-compromized or as a last resort. Now, bacteria have adapted and selected for carbapenem-destroying enzymes, known as carbapenemases, and few antibiotics remain effective against these CREs. *K. pneumoniae*, *E. coli*, *P. aeruginosa* and *A. baumannii* produce metallo-β-lactamases such as *K. pneumoniae* carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM) — enzymes that degrade numerous antibiotics containing a β-lactam ring, such as penicillins, cephalosporins and carbapenems. Bacteria carrying the genes that encode these enzymes are becoming resistant to all available penicillins, cephalosporins and β-lactamase inhibitors, including clavulanic acid and avibactam (FIG. 1). These bacteria are also resistant to virtually all other antibiotics, with the exception of colistin, an old (and somewhat toxic) polymixin class antibiotic, although even colistin resistance has now emerged in South Asia. Both KPC and NDM, as well as Verona integron-encoded metallo-β-lactamase (VIM), have been reported in *Pseudomonas* spp. In some areas of the world, including the United States, Israel, Italy, Greece and China, the emergence of bacteria that produce KPCs, which render them resistant to carbapenems, is becoming a serious threat.

A few derivatives of older antibiotic classes or combinations incorporating new β-lactamase inhibitors such as avibactam and tazobactam offer some hope in the short term. Two compounds that have reached Phase III trials — eravacycline[5], a next-generation tetracycline, and plazomicin[6], a next-generation aminoglycoside — have activity against Gram-negative organisms. The recently approved ceftazidime–avibactam[7] combination is effective against

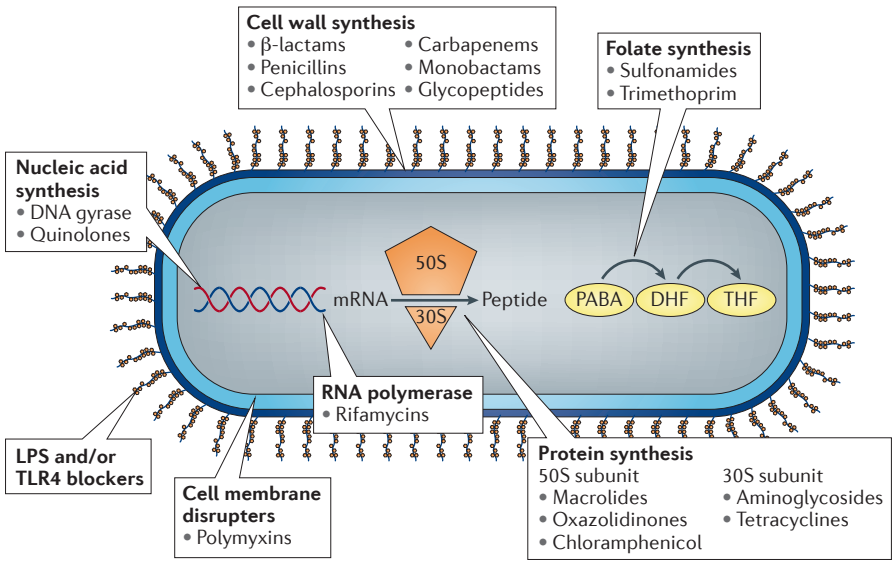


Figure 1 | **Sites of antibacterial action and mechanisms of resistance.** Antibiotics can be classified by their mechanism of action. Resistance to one antibiotic within a class can confer resistance to others with the same target. Resistance arises by two main mechanisms: random mutations during DNA replication and transfer of DNA between bacteria, often as plasmids. The transferred DNA can contain genes that confer resistance, and natural selection then favours the survival of the resistant bacteria during antibiotic treatment of a patient. DHF, dihydrofolic acid; LPS, lipopolysaccharide; PABA, para-aminobenzoic acid; THF, tetrahydrofolic acid; TLR4, Toll-like receptor 4.

several MDR Gram-negative bacteria; the ceftolozane–tazobactam[8] combination (also recently approved) has good anti-pseudomonal activity; and the aztreonam–avibactam combination[7], which is in Phase III trials, works against many organisms that produce mannose-binding lectin. However, resistance to these combinations will probably soon arise and there are no totally new chemical classes of antibiotic on the horizon for the treatment of Gram-negative bacteria.

It is therefore crucial that ways of breaking resistance to current antibiotics are found as soon as possible. One strategy to achieve this goal is to co-administer another drug with the failing antibiotic, which restores sufficient antibacterial activity. The use of such antibiotic resistance breakers (ARBs) to salvage antibiotics is exemplified by the long-standing, successful and widespread co-administration of β-lactamase inhibitors, such as clavulanic acid, with β-lactam antibiotics, such as amoxicillin[9,10]. Resistance to amoxicillin and to this combination of drugs has been slow to emerge. However, mutation of the β-lactamase TEM1 — thought to be the greatest driver of resistance to this class of antibiotics — has now occurred owing to the selection of organisms with clavulanate-insensitive β-lactamases. As noted above, several new β-lactamase inhibitors offer the hope of counteracting resistance to β-lactam antibiotics in the near term, but further exploitation of β-lactamase inhibitors may be of limited use in the longer term, as there has been a 100-fold increase in the number of known β-lactamases in the past 40 years[11].

Surprisingly, the success of β-lactamase inhibitors has not led to substantial clinical and commercial exploitation of the concept of ARBs beyond this class. Attempts to reduce resistance by blocking efflux pumps on bacterial cells — which can diminish the effectiveness of antibiotics by lowering their intracellular concentration — have been pursued for many years, so far without notable success. However, efforts continue and deserve further attention[12]. Novel combinations of existing classes of antibiotics could also be investigated; for example, macrolides may be able to synergize with β-lactams and fluoroquinolones[13–18].

This article, however, focuses on the identification of broad-spectrum ARBs by repurposing marketed drugs and nutraceuticals. ARBs selected from marketed drugs would be particularly useful as their development could be faster, cheaper and probably have a higher success rate than that for new molecules. This could be crucial, given the pressing need for strategies to tackle antibiotic resistance, the long development timelines for new antibiotics and the challenging financial environment for new antibiotic research and development. One ARB could potentially revitalize several antibiotics in a class[11], and some ARBs may even work across classes. Lethal bacterial infections might be effectively treated with far fewer compounds than would be required to replace existing antibiotics. Moreover, the concept may help to extend the lifespan of future antibiotic classes. Here, after highlighting the priority bacteria, key antibiotics to be salvaged and the properties of ARBs, we discuss a list of proposed priority candidates for further investigation and issues for their development.

Repurposing to provide ARBs

Priority antibiotics and bacteria. ARBs should be sought to salvage one or more key members of each mechanistic antibiotic class, particularly those used against Gram-negative bacteria. Thus, the antibiotics that most need ARBs are: cephalosporins and carbapenems (which disrupt cell wall synthesis); polymyxins (which disrupt cell membrane synthesis); fluoroquinolones (which disrupt DNA synthesis); tetracyclines and aminoglycosides (which disrupt protein synthesis by inhibiting the 30S ribosomal subunit); and macrolides (which disrupt protein synthesis by inhibiting the 50S ribosomal subunit).

Acquired carbapenemases have been highlighted as the greatest immediate threat to the effectiveness of the antibiotic arsenal[2]. Carbapenemases are encoded by genes that are transferable between bacteria and confer resistance to many of the most heavily used antibiotics — carbapenems and β-lactam antibiotics. The carbapenems are the last good line of defence against MDR Gram-negative bacteria, and the consensus is that extending the useful lifespan of this class of drugs is a top priority. As such, the intravenous formulation of a broad-spectrum ARB for use together with a carbapenem (or a cephalosporin) in intensive-care hospital settings should be top priority.

ARBs that are effective against *K. pneumoniae*, *E. coli*, *P. aeruginosa* and *A. baumannii,* the four Gram-negative organisms whose resistance to antibiotics is of greatest concern (all of which produce carbapenemases and are thus resistant to many β-lactam antibiotics), are of utmost importance. A secondary priority is to target Gram-positive bacteria, especially methicillin-resistant *S. aureus* (MRSA) and *Clostridium difficile* (which causes *C. difficile*-associated disease (CDAD)), as these organisms cause recurring problems that are associated with substantial death rates.

Properties and identification of potential ARBs. There are several properties that potential ARBs could possess. First, ARBs could have direct antibacterial activity, even if they are not used clinically as antibiotics. Second, ARBs could increase the efficacy of antibiotics and/or combat antibiotic resistance mechanisms. Third, ARBs could help to clear the infection by interacting with host targets to activate host defence mechanisms; for example, by blocking the pro-inflammatory Toll-like receptors (TLRs) or promoting autophagy (BOX 1). Arguably the most interesting potential ARBs are those that display more than one of these properties.

A literature review was conducted searching for potential non-antibiotic candidate drugs or nutraceuticals that are not used as antibiotics but have one or more of these three ARB properties. Drug safety and the ability to achieve a drug plasma concentration (by intravenous or oral routes) that is similar to published minimum inhibitory concentrations (MICs) for antibacterial action are also important, and combinations are more often successful if the combination partner attacks a molecular target that is different from that of the antibiotic. Therefore, these aspects were also used for prioritization. Last, the priorities above were also considered with regard to the type of infections.

For the drugs that were short-listed, a written summary was prepared of relevant mechanisms and *in vitro* and *in vivo* data, as well as any available clinical data. Then, through individual and group discussions with global experts, the strengths and weaknesses of each drug were identified. Based on these discussions, the priority drugs with the strongest evidence supporting a potential role in breaking resistance are presented in TABLES 1,2 and grouped into three categories in the discussion below: potential ARBs for Gram-negative bacteria, potential ARBs for Gram-positive bacteria and potential ARBs for both classes. Some drugs such as aspirin[19,20], diclofenac[21–23], ibuprofen[24–26], ivermectin[27,28], lauric acid or monolaurin[29,30], metformin[31–33], and vitamin D3 (REFS 34,35) were excluded owing to a lack of compelling evidence, although future research could identify these drugs as potential ARBs (TABLE 3).

Potential ARBs for Gram-negative bacteria

Ciclopirox. Ciclopirox has been used for several decades as a topical antifungal agent without the emergence of resistance. It is a broad-spectrum agent with activity against most clinically relevant dermatophytes, yeasts, and moulds. Moreover, it has antibacterial activity, although this has never been exploited clinically. Ciclopirox kills a wide range of bacteria including many Gram-negative and Gram-positive species[36].

Recently, it was reported that this drug has direct antibacterial activity against several of the high-priority MDR Gram-negative bacteria[37]. When tested against antibiotic resistant *A. baumannii, E. coli* and *K. pneumoniae*, ciclopirox inhibited bacterial growth at concentrations of 5–15 μg per ml, regardless of the antibiotic resistance status. The authors suggested that the compound inhibited the synthesis of lipopolysaccharide (LPS) in the surface coat of Gram-negative bacteria. This would be a particularly valuable mechanism, as the LPS coat protects Gram-negative bacteria from the entry of many antibiotics. Inhibition of LPS synthesis might render Gram-negative bacteria susceptible to antibiotics that are normally reserved for Gram-positive organisms.

Ciclopirox also chelates intracellular iron, which probably results in the inhibition of metal-dependent enzymes. In *Candida albicans*, ciclopirox has also been reported to alter the regulation of the genes encoding iron permeases or transporters (*FTR1*, *FTR2* and *FTH1*), a copper permease (*CCC2*), an iron reductase (*CFL1*) and a siderophore transporter (*SIT1*)[38]. Addition of $FeCl_3$ to ciclopirox-treated cells reversed the effect of the drug on gene regulation, indicating that its antifungal activity may be at least partially caused by iron limitation[38].

Other mechanistic studies have indicated that, in addition to the effects on iron, ciclopirox also downregulates nucleotide binding proteins[39] and inhibits mammalian target of rapamycin (mTOR) signalling, thereby inducing autophagy in mammalian cells[40]. It seems likely that ciclopirox would also activate autophagy in immune cells (BOX 1).

The rapid development of ciclopirox for use against bacterial infections either alone or as an ARB could be aided by the existing pharmacokinetic, metabolic, toxicological and clinical data. Ciclopirox is usually administered topically, however, owing to the interest in ciclopirox for treatment of haematological malignancies such as multiple myeloma[41,42], systemic dosing of this drug has been investigated[41]. Data from animal studies and a single human

Box 1 | Host-targeted drugs that induce autophagy may break antibiotic resistance

Autophagy eliminates unwanted constituents from cells, including pathogens, damaged organelles and aggregated proteins. During fasting or starvation, autophagy recycles cytoplasmic material to maintain cellular homeostasis. Over the past few years, an increased understanding of the pathways of autophagy has led to recognition of its role in a broad range of disease processes, including host defence against pathogens. There are several excellent reviews on the role of autophagy as a defence against microbial invasion[125,126].

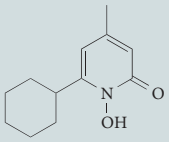
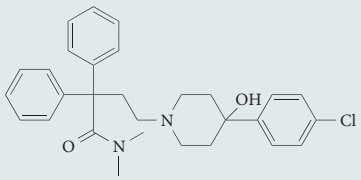
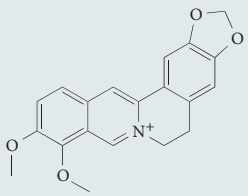
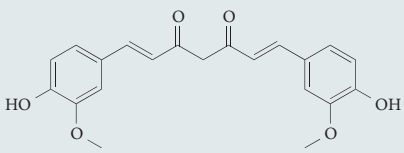
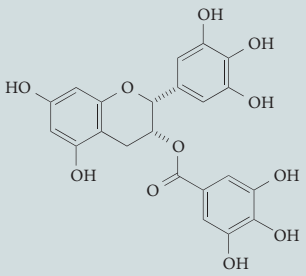
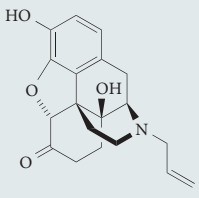
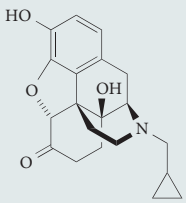
Bacteria that are degraded by intracellular autophagy include Group A *Streptococcus* spp.[127], *Salmonella* spp.[128], *Shigella* spp.[129], *Listeria monocytogenes*[130] and *Mycobacterium tuberculosis*[131–133]. However, some bacteria have evolved to subvert this process[134–136].

The best characterized protein involved in autophagy is mammalian target of rapamycin (mTOR). Autophagy is induced by direct inhibitors of mTOR or by inhibitors of pathways that activate mTOR — class I phosphoinositide 3-kinases (PI3Ks) and receptor tyrosine kinases that activate the AKT pathway — thereby repressing autophagy. Inhibitors of these enzymes may provide useful therapeutics by inducing autophagy, although none is marketed at the present time. Similarly, modulators of 5′-AMP-activated protein kinase (AMPK)[137], mitogen-activated protein kinases (MAPKs; including extracellular signal-regulated kinases (ERKs)) and the WNT signalling pathway[138] may be useful to increase autophagy and promote bacterial clearance. Drugs that inhibit some of these pathways are in development for the treatment of cancer and might prove effective in treating some infectious diseases.

Particularly intriguing is the recent observation that activation of autophagy specifically in the gut leads to systemic effects[139]. Remarkably, activation of intestinal AMPK induces autophagy in both the gut and the brain and slows systemic ageing. Activation of autophagy in the gut alone could therefore be sufficient to aid the clearance of systemic infections. This possibility is very relevant in assessing the potential of the AMPK activators, some of which have relatively low bioavailability.

It is currently unclear whether activators of autophagy would be sufficiently powerful to use without antibiotics, but they could be used as ARBs when co-administered with antibiotics, similarly to β-lactamase inhibitors. There are already autophagy-activating drugs in clinical use or under clinical investigation for other diseases. If modulation of autophagy does emerge as a useful drug approach for the treatment or prevention of bacterial diseases, it is possible that useful medicines could be repurposed from other indications.

Table 1 | **Priority compounds for repurposing as ARBs**

Compound	Class	Structure	Potential mechanisms of action
For Gram-negative bacteria			
Ciclopirox	Antifungal: used without the development of resistance for several decades		Ciclopirox inhibits the synthesis of the LPS coat of Gram-negative bacteria[37], chelates iron and regulates the genes encoding iron permeases or transporters (*FTR1*, *FTR2* and *FTH1*), copper permease (*CCC2*), iron reductase (*CFL1*) and siderophore transporter (*SIT1*). It may also contribute to antimicrobial effects[38], and it can induce autophagy[40]
Loperamide (Imodium; Janssen Pharmaceutica)	Anti-motility: used for the treatment of diarrhoeal diseases		Loperamide facilitates tetracycline uptake[45]. With cephalosporins, loperamide dissipated the electrical component ($\Delta\Psi$) of the proton motive force (PMF). In this same assay, cephalosporins selectively dissipated the transmembrane chemical component (ΔpH) of the PMF. The elimination of both $\Delta\Psi$ and ΔpH completely abolishes PMF and explains the observed synergy between loperamide and cephalosporins[45]
For Gram-positive bacteria			
Berberine	A traditional medicine in Europe, Asia and the Americas. It is used for the treatment of diarrhoea caused by *Giardia lamblia* and the Gram-negative bacteria *Escherichia coli*, *Klebsiella* spp. and *Vibrio cholerae*		Direct antibacterial action may be due, in part at least, to inhibition of Gram-positive bacterial sortase[49]. It binds to TLR4–MD2, thereby antagonizing LPS signalling[51]. Berberine inhibits TLR4–NF-κB–MIP2 signalling, thus decreasing neutrophil infiltration[53], downregulates the expression of pro-inflammatory genes (such as those encoding TNF, IL-1β, IL-6, MCP1, iNOS and COX2 (REF. 54)) and activates AMPK, thus inducing autophagy[55]
For both Gram-negative and Gram-positive bacteria			
Curcumin	A food flavouring, colouring and neutraceutical		Curcumin competes with the LPS of Gram-negative bacteria to block excessive inflammatory responses and prevent bacterial invasion. It inhibits TLR2 and TLR4 signalling[72,73], downregulates TLR expression[74,75], prevents the upregulation of IL-8 expression[79] and induces autophagy by inhibiting the AKT–mTOR pathway[71]
Epigallocatechin-3-gallate (EGCG)	EGCG is one of the most abundant polyphenols in green tea and is thought to be responsible for most of the supposed therapeutic benefits of green tea consumption		EGCG has a broad range of mechanisms, including inhibition of DNA gyrase[103], blockade of TLR4 binding[106] and signal transmission, and inhibition of conjugative transfer of the R plasmid of *E. coli*[107]
(+)-Naltrexone and (+)-Naloxone	These are selective opioid antagonists used to counter the effects of opioid overdose	(+)-Naloxone  (+)-Naltrexone 	Both compounds block TLR4–MD2 signalling[119]

AMPK, 5′-AMP-activated protein kinase; ARBs, antibiotic resistance breakers; COX2, cyclooxygenase 2; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MCP1, monocyte chemotactic protein 1; MIP2, macrophage inflammatory protein 2; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor.

oral dosing study suggest that drug safety is satisfactory for human trials of ciclopirox for the treatment of cancers[41]. On dosing radiolabelled ciclopirox to humans, 96% of the label was recovered from urine; however, a specific plasma or serum assay for ciclopirox olamine was not used in this study[43]. The authors stated that the pharmacological drug levels of ciclopirox required for anti-tumour activity are achievable even though its half-life is short, but require dosing several times a day. They noted, however, that the drug seemed to be well absorbed after oral administration. As a result of this analysis, this group sponsored a Phase I study[44], which demonstrated that oral ciclopirox olamine achieved plasma levels of 50 ng per ml after a single oral dose of 20–40 mg per m^2 and had biological activity in patients with advanced haematological malignancies. Dose-limiting gastrointestinal toxicities were observed in patients receiving the highest oral dose administered four times a day, but not at lower doses or at a less frequent dosing schedule. Dosing regimens against bacteria are likely to be shorter than those for the treatment of cancer, and gastrointestinal toxicity is less likely if the drug is administered intravenously as an ARB against life-threatening bacteria in a hospital setting, where the need for ARBs is greatest.

Ciclopirox has at least two of the three properties suggested for an ARB as it is directly antibacterial and it induces the host defence response by causing autophagy. However, data are required on whether or not this drug is effective in combination with antibiotics. Moreover, its activity against a broad range of bacteria needs investigation. The appropriate clinical dose can then be calculated, and safety studies will be required to assess the therapeutic index, particularly for intravenous dosing. Concomitant activity against *C. albicans* is a bonus, because *Candida* spp. are a leading cause of catheter-associated infections, which have high mortality rates.

Loperamide. This μ-opioid receptor agonist has long been used as an anti-motility agent in the treatment of diarrhoeal diseases. Ejim *et al.*[45] recently showed that loperamide, which has no antibacterial activity per se, acts synergistically with several classes of antibiotic. They screened off-patent non-antimicrobial drugs as a source of molecules that might synergize with antibiotics at sub-MIC concentrations. Loperamide, at a concentration of 16 μg per ml or greater, increased the antibacterial efficacy of eight tetracycline antibiotics against Gram-negative pathogens (but not Gram-positive pathogens) and was active in combination with the broad-spectrum tetracycline-class antibiotic minocycline in a mouse model of salmonellosis. In addition to tetracyclines, loperamide increased the efficacy of cephalosporins (but not other cell-wall-directed antibiotics) and the outer-membrane-permeating antibiotic polymyxin B *in vitro*. The authors concluded that it is improbable that the synergy observed *in vivo* was the result of the antiperistaltic activity of loperamide, as the potentiation was observed at concentrations of minocycline that do not impair bacterial growth even upon prolonged exposure.

Loperamide has also been shown to sensitize Gram-negative bacteria to 'Gram-positive antibiotics' (REF. 46). In the presence of loperamide, the aminocoumarin antibiotic novobiocin inhibited the growth of *E. coli*. Loperamide may alter the cell shape and small-molecule permeability of *E. coli*, similar to the mechanism through which colistin boosts the effectiveness of vancomycin and rifampin[47]. The authors suggested that the altered cell shape may cause dysregulation of the influx and efflux machinery of Gram-negative bacteria and thereby enable the accumulation of otherwise-excluded antibiotics. This concept could be further exploited by screening current drugs and nutraceuticals for similar effects against a wide range of Gram-positive antibiotics. One concern is that repurposing Gram-positive antibiotics for Gram-negative pathogens could promote resistance to these agents by transfer of resistance determinants, but in view of the greater threat of Gram-negative organisms this may be a risk worth taking.

Loperamide is not orally bioavailable, but it could be used orally as an ARB to treat gut infections, such as diarrhoeal diseases, and intravenously for other infections if it is proven to be safe. Although loperamide is an opioid, it has no opiate-like effects when administered orally or intravenously. It does not cross the blood–brain barrier because it is subject to efflux by P-glycoprotein; therefore, intravenous loperamide could not be used with inhibitors of P-glycoprotein.

Table 2 | **ARBs for each main antibiotic class**

Drug (target)	ARBs for Gram-negative bacteria	ARBs for Gram-positive bacteria
Carbapenems, cephalosporins and penicillins (cell wall synthesis)	• Ciclopirox • Loperamide (intravenous) • Macrolides • EGCG • Naloxone, naltrexone and curcumin (for gut pathogens and LPS-driven endotoxic shock)	• Curcumin • EGCG • Berberine
Polymyxins (cell membrane)	Loperamide	NA
Aminoglycosides (protein synthesis)	None identified	NA
Fluoroquinolones (nucleic acid synthesis)	None identified	Curcumin
Tetracyclines (protein synthesis)	Loperamide	Curcumin
Glycopeptides (cell wall synthesis)	NA	Naloxone, naltrexone and curcumin (with vancomycin or metronidazole for the treatment of CDAD)
Macrolides (protein synthesis)	NA	None identified
'Gram-positive antibiotics'	Loperamide	NA

ARBs, antibiotic resistance breakers; CDAD, *Clostridium difficile*-associated diarrhoea; EGCG, epigallocatechin-3 gallate; LPS, lipopolysaccharide; NA, not applicable.

Potential ARBs for Gram-positive bacteria

Berberine. The plant-derived isoquinoline alkaloid berberine has a long history of use for the treatment of several conditions. In particular, it has been used in traditional medicine in Europe, Asia and the Americas to treat diarrhoea caused by *Giardia lamblia* as well as the Gram-negative bacteria *E. coli, Klebsiella spp.* and *Vibrio cholerae*. It has broad-spectrum direct antibacterial activity against staphylococcal, streptococcal and enterococcal species, including MDR

strains of *Mycobacterium tuberculosis* and MRSA. *In vitro*, berberine is about ten-times more potent against Gram-positive bacteria than Gram-negative. Its ability to kill *Streptococcus pneumoniae* and *S. aureus* may be particularly relevant as these are among the most common bacterial causes of pneumonia.

When tested alone *in vitro* against clinical isolates of MRSA[48], berberine showed moderate activity against all strains tested, with MICs of 32–128 μg per ml.

Table 3 | **Potential drugs excluded as high priority, based on the current lack of data**

Candidate drug for repurposing	Current approved indication or common usage	Summary of evidence	Additional information required
Aspirin	Pain, inflammation and anti-platelet	• *In vitro*: reduces resistance to aminoglycosides in *Klebsiella pneumoniae* and enhances the susceptibility of *Helicobacter pylori* to antibacterials[140]; however, it induces resistance to many other antibiotic classes[141]. • *In vivo*: reduces the incidence of *Staphylococcus aureus* in a rabbit model of aortic valve endocarditis[142], is additive or synergistic if combined with vancomycin in a rabbit model of endocarditis caused by *S. aureus*[143] and reduced the prevalence of nasal *S. aureus*[19]and *S. aureus* bacteremia[20] in patients receiving haemodialysis	Confirmation of activity alone and in synergy with antibiotics against antibiotic-resistant MRSA. A safety assessment is needed for intravenous dosing
Diclofenac	Pain and inflammation	• *In vitro*: directly antibacterial against antibiotic-sensitive and antibiotic-resistant clinical isolates of *S. aureus*, *Listeria monocytogenes*, *Escherichia coli* and *Mycobacterium* spp., including anti-plasmid activity[21,22]. Synergistic in combination with streptomycin against *E. coli* and *Mycobacterium* spp., and with gentamicin against *Listeria* spp.[144]; blocked both cAMP-activated and Ca^{2+}-activated chloride secretion in intestinal epithelial cells infected with *Vibrio cholerae*[23] • *In vivo*: Effective in mice in treating infections of *V. cholerae*[23], *Salmonella* spp.[145], *Listeria* spp.[144], and *Mycobacterium tuberculosis*[146]	The MIC_{90} needs to be improved — it is typically 100 μg per ml, which is two orders of magnitude above the C_{max} exposure achieved with a 50 mg oral dose in humans. Direct or synergistic antibacterial actions against drug-resistant Gram-negative bacteria should be investigated at safe doses
Ibuprofen	Pain and inflammation	• *In vivo*: mice infected with *M. tuberculosis* that were treated with ibuprofen lived longer than control animals[24,25]. Oleocanthal, the active constituent of olive oil, affects the same receptor as ibuprofen and has antibacterial activity[26]	The *in vitro* and *in vivo* activity against the major drug-resistant Gram-negative bacteria, alone and with antibiotics, should be explored. A safety assessment for intravenous dosing is also required
Ivermectin	Clinical and veterinary nematode infections	• *In vitro*: inhibits growth of *Chlamydia trachomatis* in epithelial cells[27] • *In vivo*: improved survival in mice subjected to 'endotoxic shock' with a lethal dose of LPS[28], decreased levels of inflammatory cytokines[28] and activated autophagy[147]	The effects of ivermectin in combination with antibiotics should be investigated against drug-resistant Gram-negative bacteria. Safety for intravenous dosing should also be assessed
Lauric acid (active metabolite is monolaurin)	Neutraceutical (coconut oil)	• *In vitro*: inhibits the synthesis of most staphylococcal toxins and other exoproteins[29]. Blocks induction, but not constitutive synthesis, of β-lactamase[30]	An exploration of *in vitro* and *in vivo* activity against the major drug-resistant Gram-negative bacteria, alone and with antibiotics, is necessary. A safety assessment is also required for both oral and intravenous dosing
Metformin	Anti-diabetic	• *In vivo*: enhances phagocytosis by macrophages in a mouse model of *E. coli* lung infection[148]. AMPK activation with metformin increased the survival rate in mice challenged with LPS in an endotoxemia model[32], reduced cholera-toxin-mediated increases in intestinal chloride secretion[33] and decreased disease severity in mice and humans infected with *M. tuberculosis*[149,150]	For intestinal infections, the synergy with antibiotics against bacteria such as *V. cholerae* and *E. coli* needs to be assessed, which may be possible at the current approved dose levels of metformin. For systemic infections, the plasma levels required for systemic effects to break antibiotic resistance should be defined, and their safety determined. It must be determined whether AMPK activation in the gut is sufficient for systemic synergy with antibiotics[139]
Vitamin D	Calcium absorption and bone health, and tuberculosis[151]	• *In vitro*: inhibits mycobacterial entry and survival within macrophages through the induction of autophagy[34,152]. IL-32 stimulates the immune system to kill *M. tuberculosis*, but only in the presence of sufficient vitamin D3 levels[35]	Studies on IL-32 and vitamin D3 should be extended to other bacteria. The levels of vitamin D3 required *in vivo* must be determined and the safety of the levels required for both oral and intravenous dosing assessed

AMPK, 5′-AMP-activated protein kinase; cAMP, cyclic AMP; C_{max}, maximum concentration; IL-32, interleukin-32; LPS, lipopolysaccharide; MIC_{90}, the minimum concentration that inhibits 90% of bacterial isolates; MRSA, methicillin-resistant *S. aureus*.

Ninety per cent inhibition of MRSA growth was obtained with a concentration of 64 μg per ml or less of berberine. These effects may be due, at least in part, to inhibition of the Gram-positive bacterial sortase enzyme, an important anti-virulence target[49]. In the Gram-negative *E. coli*, berberine targets assembly of the cell division protein FtsZ[50]. It inhibits the assembly kinetics of the Z-ring and perturbs cytokinesis. It also destabilizes FtsZ protofilaments and inhibits the FtsZ GTPase activity. Berberine binds to FtsZ with high affinity (dissociation constant (K_D) = 0.023 μM) and thus halts the first stage in bacterial cell division.

In vivo, berberine protected mice challenged with *Salmonella typhimurium*: 50% of the mice that did not receive berberine treatment died by the end of the eighth day after infection, whereas, with doses of 10, 20, 30 and 40 mg per kg of berberine, 60, 60, 70 and 90% of the infected mice survived to the eighth day, respectively[51].

Encouragingly, another study reported that bacteria are poor at generating resistance to berberine[52]. The MICs of bacterial cultures (*E. coli, S. aureus, Bacillus subtilis, Proteus vulgaris, S. typhimurium* and *P. aeruginosa*) did not increase over 200 generations despite treatment with berberine at a concentration of 50% of its MIC.

There is also evidence that berberine could be an ARB[48]: berberine markedly lowered the MICs of ampicillin and oxacillin against MRSA; an additive effect was found between berberine and ampicillin; and a synergistic effect was found between berberine and oxacillin[48]. In the presence of 1–50 μg per ml berberine, levels of MRSA adhesion and intracellular invasion were notably decreased compared with the vehicle-treated control group. These results suggest that berberine may have direct antimicrobial activity, the potential to restore the effectiveness of β-lactam antibiotics against MRSA, and the ability to inhibit MRSA adhesion and intracellular invasion. Berberine may also have ARB activity by increasing the host defence response. It protects against LPS-induced intestinal injury in mice by inhibiting the TLR4–NF-κB–MIP2 (Toll-like receptor 4–nuclear factor κB–macrophage inflammatory protein 2 (also known as CXCL2)) pathway in ileal cells and decreasing neutrophil infiltration[53]. Berberine can also act as an LPS antagonist by binding to TLR4–MD2 (also known as LY96) complexes and blocking LPS–TLR4 signalling in murine macrophage-like cells (RAW 264.7)[51]. This may explain its reported effectiveness against Gram-negative bacteria-induced diarrhoeal diseases despite its lower *in vitro* activity against Gram-negative bacteria than against Gram-positive species.

During infection, berberine drives suppression of pro-inflammatory responses through activation of 5′-AMP-activated protein kinase (AMPK) in macrophages[54], a property that could also lead to antibacterial activity via autophagy. Mechanistic studies have shown that berberine downregulates expression of proinflammatory genes such as tumour necrosis factor (*TNF*), interleukin-1β (*IL1B*), *IL6*, monocyte chemotactic protein 1 (*MCP1*; also known as *CCL2*), inducible nitric oxide synthase (*iNOS*; also known as *NOS2*), and cyclooxygenase 2 (*COX2*; also known as *PTGS2*) (REF. 54).

Metformin, a commonly used antidiabetic agent, also activates AMPK, and so berberine has been studied as an antidiabetic agent[55,56]. In patients with type 2 diabetes, berberine has been reported to have an efficacy equivalent to that of metformin[57]. Berberine has also been investigated as a chemotherapeutic agent, and so its potential for cell toxicity would need to be accounted for if it were to be used in any human studies as an ARB. The bioavailability of berberine is reportedly less than 5% owing to poor absorption and rapid clearance. Berberine seems to be subject to P-glycoprotein-mediated efflux from the intestine and liver. Absorption has been enhanced with sodium caprate, a medium chain fatty acid found in milk fat and coconut oil. However, bioavailability issues do not seem to have been limiting in the human studies reported above.

Potential ARBs for both bacterial classes

Curcumin. Curcumin is a constituent of the popular spice turmeric, which has been used for centuries in both cooking and traditional medicine across the Indian subcontinent. It is currently being investigated for efficacy against a number of diseases, including cancer, and against mechanisms of ageing[58,59].

Curcumin has direct antibiotic activity at concentrations of 125–1,000 μg per ml against a broad range of bacteria, including some Gram-negative species (including *E. coli, P. aeruginosa, V. cholerae, S. aureus and B. subtilis*)[60]. Although curcumin had some antibacterial effects against *Helicobacter pylori* infections *in vitro*[61] and in animal studies[62], human studies have produced mixed results[63–65].

There is also evidence supporting use of curcumin against the Gram-positive organism *C. difficile*. *In vitro*, curcumin inhibited the growth of 21 strains of *C. difficile* at a concentration of 128 μg per ml, which is obtainable in the colon through ingestion of food or by dosage in capsules[66]. In clinical practice, ingestion of 4 g per day would achieve this concentration in the gut[66]. In regions where curcumin is a regular dietary ingredient it is typically consumed at 2–4 g per day.

Curcumin also synergizes with antibiotics. In combination studies with cefaclor, cefodizime, or cefotaxime, concentrations of 0.1–1.0 μg per ml reduced the MIC values by three- to eightfold against diarrhoea-causing bacteria, such as *E. coli* and *V. cholerae*, as well as against another Gram-negative species, *P. aeruginosa,* and the Gram-positive *S. aureus*[67]. Against MRSA, curcumin potentiated the antimicrobial action of cefixime, cefotaxime, vancomycin, tetracycline, oxacillin, ampicillin, ciprofloxacin and norfloxacin[68,69].

Numerous potential mechanisms of action have been reported, including inhibition of sortase[70]. Curcumin also induces autophagy by inhibiting the AKT–mTOR pathway[71]. Its chemical structure (a polyphenol with the ability to bind to many proteins through ionic and hydrogen bonds) may explain its promiscuous activity (TABLE 1).

In host-defence studies, curcumin blocks the binding of the LPSs from Gram-negative bacteria to MD2 in the TLR4–MD2 complex[72,73] and downregulates expression of intestinal TLR2, TLR4 and TLR9 (REFS 74,75). It also decreases the production of TNF, IL-1, IL-2, IL-6, IL-8 and IL-12, MCP1 and migration and invasion-inhibitory protein[76–80]. The ability of curcumin to block the interaction between MD2 and bacterial proteins could also explain its efficacy in treating Gram-positive infections. *C. difficile* is a Gram-positive species with no LPS coat, but its surface layer proteins are recognized by the MD2 component of the TLR4–MD2 complex in monocytes and epithelial cells, stimulating NF-kB activation and causing apoptotic intestinal epithelial cell detachment[81,82].

Through the inhibition of NF-κB[83], curcumin prevents the upregulation of IL-8 expression in response to infection[84]. IL-8 levels are elevated in patients with severe *C. difficile* colitis[85,86]; in these patients, disease severity correlates with increased levels of IL-8, IL-6 and eotaxin, and IL-8 expression correlates with treatment failure after metronidazole and vancomycin therapy[87,88]. Curcumin may be an effective ARB for patients with *C. difficile* infections by modulating their gut cytokine response, especially in those patients with relapsing infection.

Well-controlled oral intervention trials studying the use of curcumin to treat *C. difficile* infections are lacking. In one trial, the drug, in the form of turmeric, was dosed by enema[89]. In this trial, the turmeric enemas were as effective as vancomycin enemas for treating *C. difficile* colitis — the infection was eradicated in 76% and 83% of patients, respectively, compared with 66% in the placebo group. At 21 days post-treatment, clinical severity was reduced by 60% in the vancomycin and turmeric groups, compared to a reduction of 38% in the placebo group. Recurrence developed in 10% of patients treated with vancomycin, 9% of those in the turmeric group and 29% of patients who received the placebo.

Some authors have reported that curcumin has poor bioavailability[90], which is due to a combination of adverse properties: poor aqueous solubility, poor absorption and rapid conjugative clearance. However, neuroscientists have reported therapeutic levels in the brain following oral dosing of either curcumin or preparations with enhanced bioavailability[91]. Brain levels reached 3 μM for curcumin and 6 μM for tetrahydrocurcumin[92] and positive effects have been reported in animal models of Alzheimer disease[91,93]. Similar efficacy was observed after intraperitoneal dosing in a model of cerebral ischaemia in rats[73], suggesting that bioavailability may not be limiting.

Further exploration of the ability of curcumin to synergize with antibiotics[60] and potentially reduce antibiotic resistance in bacterial pathogens of the gastrointestinal tract is warranted. In view of the diversity of opinions on bioavailability, it would seem wise to focus additional oral investigations on those bacteria that cause diarrhoeal diseases and/or gain entry through the gut. These can over-stimulate TLR4 in particular, causing a 'cytokine storm' and excessive inflammation that aids their entry into sterile gut wall tissues and the bloodstream. The ability of curcumin to dampen down this excessive inflammatory response may lead to preventative or treatment options for gut-invading Gram-negative bacteria, such as *Salmonella* spp., *Shigella* spp., and *E. coli*, as well as the Gram-positive *C. difficile*. Intravenous doses of curcumin may be effective against systemic infections in which the cytokine storm has devastating effects, such as Gram-negative bacteria-mediated sepsis.

Epigallocatechin-3-gallate (EGCG). Epigallocatechin-3-gallate (EGCG) is one of the most abundant polyphenols in green tea and is thought to be responsible for most of its supposed therapeutic benefits. EGCG has been extensively studied in many disease areas and written about in several thousand scientific publications, with most published over the past two decades. The anti-infective effect of green tea was first reported more than 100 years ago by Major J. G. McNaught, an army surgeon who showed that green tea killed the Gram-negative organisms that lead to typhoid fever (*Salmonella typhi*) and brucellosis (*Brucella melitensis*)[94].

Two recent comprehensive reviews[95,96] have detailed mild antibiotic activity of EGCG alone *in vitro* and substantial synergy of EGCG with a broad range of antibiotics to treat both Gram-positive and Gram-negative organisms, particularly if antibiotic resistance is present. EGCG has positive synergistic effects, although the occasional adverse effect on resistance *in vitro* has been reported[101].

EGCG can sensitize MRSA to all types of β-lactam antibiotics, including benzylpenicillin, oxacillin, methicillin, ampicillin, carbapenems and cephalexin[97–100]. The fractional inhibitory concentration (FIC) indices of β-lactams tested against 25 isolates of MRSA ranged from 0.126 to 0.625 when used in combination with EGCG at 6.25, 12.5 or 25 μg per ml. When used in combination with three carbapenems that do not usually show strong activity against MRSA, EGCG showed additive and synergistic effects, bringing potency to within a useful range: the MICs of imipenem in the presence of EGCG at 3.125, 6.25, 12.5 and 25 μg per ml were restored to the susceptibility breakpoint (<4 μg per ml) for 8, 38, 46 and 75% of the MRSA isolates, respectively, thus rendering these bacteria 'susceptible' (REF. 101). EGCG is able to break the resistance of many bacteria to β-lactams and carbapenems, and it also increased the efficacy of inhibitors of protein or nucleic acid synthesis[102]. However, EGCG may have adverse effects when combined with glycopeptide antibiotics (vancomycin or teicoplanin)[101]. Importantly, EGCG seems to have no adverse effects on commensal bacteria[103].

EGCG may also be useful in treating Gram-negative infections. *In vitro*, EGCG killed MDR and extended-spectrum β-lactamase (ESBL)-producing strains of *E. coli* that were isolated from urinary tract infections[104]. *In vivo*, green tea and EGCG dose-dependently abrogated endotoxin-induced high mobility group protein B1 (HMGB1) release from murine macrophage-like RAW 264.7 cells and dose-dependently protected mice against lethal endotoxemia and sepsis[105]. The authors noted that doses of EGCG given orally to septic mice (4 mg per kg, which is 10 mM) were comparable to those achievable in humans after ingestion of a few cups of green tea (1 mM). Importantly, delayed and repeated administration of EGCG beginning 24 hours after onset of sepsis substantially rescued mice from lethal sepsis, supporting a therapeutic potential for EGCG in the clinical management of sepsis.

The mechanisms by which EGCG exerts its effects on bacteria seem to be very broad; this is probably due to its chemical structure, which contains phenolic groups capable of making ionic and hydrogen bonds with multiple proteins. EGCG binds to the peptidoglycans of the bacterial cell wall and inhibits penicillinase activity, protecting penicillins from inactivation[106]. It also alters the cell wall of *S. aureus*[107]. It has been suggested that the ability of EGCG to reverse methicillin resistance is mediated by inhibition of the synthesis of the penicillin-binding protein 2a (PBP2a) as well as inhibition of β-lactamase secretion[97]. In addition, EGCG inhibits DNA gyrase[108], dihydrofolate reductase[102] and specific reductases (FabG and FabI) in bacterial type II fatty acid synthesis[109]. EGCG also blocked *H. pylori* binding to TLR4 on gastric epithelial cells[110], inhibited conjugative transfer of the R plasmid in *E. coli*[111] — which could lead to decreased sharing of antimicrobial genes between bacteria — and inhibited the activity of the streptococcal efflux pump Tet(K), which is involved in resistance to tetracycline[112]. However, the effect of EGCG on a range of bacterial efflux pumps needs further definition. Additionally, EGCG activates host defence and, therefore, it may be effective at lower plasma concentrations than would be expected by simple extrapolation from *in vitro* data. EGCG also increases autophagy[113,114], possibly through activation of AMPK[115].

Human trials of EGCG in combination with antibiotics are required. EGCG has relatively poor bioavailability in animals and it is unclear whether plasma levels in humans would be sufficiently high to exert a synergistic effect with antibiotics[116]. Prodrugs of EGCG could improve bioavailability[117,118]. However, EGCG might be most useful as an ARB in topical infections, such as MRSA, and possibly as an oral treatment for gastrointestinal infections. In addition, EGCG could be useful as an intravenous agent combined with carbapenems or other antibiotics against diseases caused by systemic MRSA infection, such as pneumonia, septicemia and urinary tract infections.

(+)-naloxone and (+)-naltrexone. The opioid antagonist (−)-naloxone and the non-opioid (+)-naloxone inhibit TLR4 signalling and block the MD2–TLR4-mediated inflammatory side effect of opioids. They may bind preferentially to the LPS binding pocket of MD2 rather than to TLR4 (REF. 119). (+)-naloxone has no known off-target effects[120], however, its half-life is short, whereas the structurally related (+)-naltrexone has a half-life of 4–6 hours in humans[121].

These (+)-isomers are devoid of opioid-like activity, and theoretically they could be used to treat some bacterial infections, as blocking TLR4–MD2 in the gut could prevent bacterial LPS from triggering a cytokine storm driven by IL-6 and IL-8 and thereby prevent invasion by gut pathogens. These or other opioid antagonists could be useful if co-administered orally with antibiotics to treat *E. coli* or *Shigella* spp. intestinal infections or to prevent CDAD in the elderly. They could also be useful if administered intravenously for the treatment of LPS-driven systemic endotoxic shock because of their potential to block the release of pro-inflammatory cytokines.

Conclusions and next steps

Several potential ARBs are available for β-lactam antibiotics (carbapenems, cephalosporins and penicillins), which is the most important class of antibiotic for the treatment of antibiotic-resistant Gram-negative bacteria. Several of these ARBs disrupt the bacterial cell wall, which contains polyanionic LPS and is stabilized by the cross-bridging of divalent cations[122]. Drugs that target these divalent cations destabilize the membrane, increase its permeability and allow access of molecules that were partially or fully excluded. Indeed, several polycation antibiotics — for example, polymyxins, aminoglycosides and dibasic macrolides such as azithromycin — act through this mechanism[123] and these are ARBs themselves when co-administered with β-lactam antibiotics. In addition to potentially salvaging our best Gram-negative antibiotics, this approach may also make 'Gram-positive antibiotics' useful against Gram-negative bacteria. Further careful screening of polycation molecules in the drug pharmacopeia may identify new ARBs of this type.

No compelling ARBs were identified for two classes of antibiotics that are particularly useful, the fluoroquinolones and the aminoglycosides, although a report of successful use of EDTA with gentamycin may indicate that EDTA could be used as an ARB[124]. Future research aimed at identifying ARBs for these classes could be highly valuable.

In the reviewed literature, most of the potential ARBs discussed above are shown to be effective as directly antibacterial and/or additive to antibiotics at concentrations of 25 μg per ml or lower, which is the level required for interest by consortia such as the Innovative Medicines Initiative (IMI)'s ENABLE project, a European Union initiative that supports new drug development of antibacterials against Gram-negative organisms. Ciclopirox, loperamide, curcumin, EGCG and berberine are potential ARBs with encouraging data at 25 μg per ml. Most of the drugs considered in this Perspective have direct antibiotic activity: sometimes they exhibit additive effects with antibiotics, and sometimes they synergize with co-administered antibiotics at 0.50–50 μg per ml. For the treatment of systemic infections, the maximum dose of drug approved for use in humans must, at minimum, achieve this level of exposure at the maximum concentration (C_{max}). For topical (including gastrointestinal) infections, C_{max} may not be relevant because high local concentrations of both drug and antibiotic will be present, with a much higher probability of achieving therapeutic concentrations at the relevant site. The first application of ARBs to reach the clinic would almost certainly be in topical and gastrointestinal infections, although the most urgent clinical need is for intravenous agents against Gram-negative bacteria. The combination of two known drugs with known pharmacological, pharmacokinetic and safety profiles is possibly the best-case scenario for low-risk drug development.

The data on the use of these molecules as ARBs come from many different laboratories using diverse methodologies and often give a range of potencies for each molecule. The data need to be confirmed against the current most lethal strains to enable calculation of the plasma concentrations of ARBs that will be required. It will then be necessary to conduct safety assessments to determine a therapeutic index for each ARB. The agents considered in this Perspective are all ingested by humans today, so they already have a lengthy safety record; however, their safety does need to be confirmed for the particular doses, combinations and routes of administration that would be used to treat bacterial infections.

Additionally, there are regulatory considerations that need to be addressed (BOX 2). Will regulatory authorities require three-way clinical trials, comparing each drug individually with the combination? Do we have the time to perform such perfect clinical trials? The Ebola epidemic in West Africa has shown that society is now amenable to fast-track development of new drugs when a global emergency dictates it.

Profit margins for combinations of known drugs may be low even if they are lifesavers. Pharmaceutical or biotechnology companies are unlikely to invest in this approach, although those that currently sell antibiotics may be able to preserve sales and reach new patents by adding an ARB in a new combination. In particular, as no ARBs have been identified for fluoroquinolones

Box 2 | Regulatory pathways for repurposed drugs

In the United States, the US Food and Drug Administration (FDA) has in place a regulatory pathway, 505(b)(2), that applies to a new use or new formulation of an approved drug. It allows the applicant to use the existing safety, pharmacology and toxicology data for regulatory purposes, provided that the doses and exposure used are the same or lower. The application can refer to published literature, product labels and product monographs. Parallel regulations apply to investigational new drug filings.

Europe and other regions have similar regulations. The intellectual property could not be protected with a composition of matter claim, but in many countries a 'method of use' patent could be filed for the discovery of a new indication for an old drug that is novel, unexpected and of value to humanity. Together with a use claim, the development of a new formulation, possibly incorporating a different dose or route of administration, can further support market exclusivity.

Another possibility is to use repurposed drugs off-label. The properties of a repurposed drug could be publicized through scientific literature and conferences. If the appropriate formulation is the same, the drug could be used without formal regulatory approval for the secondary use. However, although a physician may prescribe a drug for a use other than the approved indication, drug companies have been sanctioned severely for marketing products along these lines. In addition, some payers, under certain conditions, restrict the reimbursement of products that are used off-label; the prescribing physician also incurs a greater element of product liability. Regulatory approval avoids these problems and may also be preferable as it safeguards standards of quality.

and aminoglycosides, a screening campaign to find ARBs for these antibiotics could be commercially viable if supported by 'method of use' patents (BOX 2). However, in general, unless a new economic model is developed for antibiotics, the development of ARBs will have to be pursued by government, public sector or philanthropic agencies, or combinations of these.

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FURTHER INFORMATION
WHO — antimicrobial resistance: global report on surveillance 2014: http://www.who.int/drugresistance/documents/surveillancereport/en/

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