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The potential impact of coinfection on antimicrobial chemotherapy and drug resistance

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Abstract

Across a range of pathogens, resistance to chemotherapy is a growing problem in both public health and animal health. Despite the ubiquity of coinfection, and its potential effects on within-host biology, the role played by coinfecting pathogens on the evolution of resistance and efficacy of antimicrobial chemotherapy is rarely considered. In this review, we provide an overview of the mechanisms of interaction of coinfecting pathogens, ranging from immune modulation and resource modulation, to drug interactions. We discuss their potential implications for the evolution of resistance, providing evidence in the rare cases where it is available. Overall, our review indicates that the impact of coinfection has the potential to be considerable, suggesting that this should be taken into account when designing antimicrobial drug treatments.

Keywords

drug resistance; coinfection; immune modulation; resource competition; parasite interactions

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tim.2015.05.002.

Classifying mechanisms of pathogen interactions

The spread (see Glossary) of chemotherapy-resistant pathogens is a serious global problem [1], affecting our ability to control pathogens ranging from parasites to viruses. Infected individuals are often coinfected, either by multiple strains of the same pathogen or by different species of pathogen. Classic examples include the multiplicity of strains typically identified in malaria infections [2] and coinfections involving human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (TB) [3]. Here, we present an overview of the potential ways by which coinfection might affect the outcome of chemotherapy, focusing on the question of the evolution of drug resistance.

One way to classify the diversity of possible interactions between pathogens is to set them on a spectrum of synergistic to antagonistic. In synergistic interactions, the within-host growth rate of one parasite will increase in the presence of the other, while in antagonistic interactions, the presence of one pathogen will limit the growth rate of the other. Examples of the former might include HIV–hepatitis C virus (HCV) [4] and HIV–malaria [5–7]; examples of the latter might be multiple strains of malaria [8]. It is also possible that coinfecting pathogens do not interact, but as this is unlikely to affect the evolution of resistance it is not discussed further in this review. It should be noted, however, that the degree to which pathogens interact is often unclear, and the available evidence is possibly controversial. The type of interaction broadly determines the impact of coinfections on resistance evolution: while synergistic interactions tend to promote resistance, antagonistic interactions hinder the evolution of resistance (see below).

This review is organized around the two main mechanisms that might shape the outcome of chemotherapy: (i) immune modulation (whereby the presence of the coinfecting pathogen can affect immune function), and (ii) resource modulation (where the coinfecting pathogen can have effects on resource availability for the focal pathogen) – Table 1 and Figure 1 give examples. For both mechanisms, we provide an overview of their potential to affect the emergence and spread of drug resistance across a range of pathogens, distinguishing between synergistic and antagonistic interactions where possible. It is important to note that for many pathogens, multiple mechanisms may apply; additional, less clearly classified mechanisms may also be involved (Boxes 1 and 2). Finally, while there may be clear evidence of interaction, the exact mechanism in play is frequently unknown.

Immune modulation

Pathogens attacking hosts are confronted by the immune system, and often the immune responses stimulated by one pathogen interact with those stimulated by a coinfecting pathogen. This type of interaction can be either synergistic or antagonistic, depending on pathogen identity and type of immune response.

Synergistic interactions: immune-mediated facilitation

When coinfection occurs, one or both pathogens may suppress the immune response. This suppression may facilitate the spread of drug-resistant mutants of the coinfecting pathogen via several routes. First, reduced immune-mediated killing of pathogens may lead to higher

pathogen replication, which can increase the probability of the emergence of *de novo* resistance (e.g., HIV–malaria coinfection [5]). Second, the reduced efficacy of the immune system may increase the frequency of symptomatic infections (in the absence of immunopathology) and hence the use of antimicrobials (e.g., HIV–herpes simplex virus 2 coinfection [9]), which will increase the selective pressure for resistant mutants and potentially the spread of resistant pathogens. Third, reduced immune-mediated killing may allow the replication of drug-resistant strains bearing a high fitness cost (which would otherwise be outcompeted by fitter sensitive strains, e.g., HIV–TB coinfection [10]). Similarly, impaired immune control may increase the danger of a recrudescence of partially resistant pathogen populations after therapy has ended. Such partially resistant pathogen populations are often selected for during therapy, and might be present after treatment [11]; with an effective immune response they would be rapidly eliminated, but an immunosuppressive coinfection may allow for their proliferation [12]. The impact of HIV coinfection on drug-resistant TB and malaria, on which recent major strides in research have been made, are classic examples of how an immunosuppressive pathogen can exacerbate resistance problems.

For TB, Dye *et al.* [13] suggest several mechanisms for why HIV coinfection increases the risk of drug resistance, including increased mycobacterial burden [14] (causing an increased risk of *de novo* resistance mutations), lower fitness thresholds [10] (allowing the spread of resistant strains with low fitness), and reduced drug absorption of anti-TB drugs in the presence of HIV [15] (facilitating selection for partially resistant strains).

For malaria, it has been suggested that an HIV-mediated increase in replication of the malaria parasite promotes *de novo* resistance [5]. Indeed, an increased prevalence of resistant malaria parasites has been found in HIV-positive versus HIV-negative pregnant women [16]. The mechanisms promoting malaria drug resistance in HIV-coinfected hosts are expected to be similar to those promoting TB drug resistance in HIV–TB infections, but evidence is largely lacking.

Although HIV presents a rather extreme case of immune modulation, coinfections with other pathogens can have similar effects on the efficacy of chemotherapy and the evolution of drug resistance. For instance, it has been shown that helminth species that suppress the interferon-γ (IFN-γ) response lead to a higher pathogen load of coinfecting microparasites in mice [17]. Recent work, also in mice, has indicated that helminths can impair antiviral immunity directly, and that these effects can be long-lived and have implications for individual- and community-level resistance ecology [18]. In humans, measles infection can considerably suppress the immune system, thereby increasing the pathogenicity of coinfecting microbes [19, 100]. Similarly, malaria infections in young children are associated with an increased risk of invasive bacterial infections, possibly through malaria-induced spleen dysfunction [20]. Lastly, epithelial cell damage and/or dysfunctional innate immune responses triggered by influenza infections may cause a transiently elevated incidence of bacterial coinfections [12,21]. Such coinfections, in turn, may increase the need for antibiotics, particularly following a primary disease episode, and thus increase potential selection for resistance.

Another possible mechanism of immune manipulation by the first-arriving pathogen is illustrated by superinfections with two TB strains: *in vivo* experiments have suggested that superinfecting TB strains are shuttled to pre-existing granulomas caused by prior TB infections. In these granulomas, the new infecting cells may avoid immune surveillance. Local competition between strains may also occur, but this phenomenon does seem to assist the superinfecting strain in evading the immune response [22].

More generally, most pathogens evade the immune system, and many of them do so by impairing its function rather than by simply escaping recognition [23]; recent research has shed better light on the underlying mechanisms [11,12,19,22]. The quantitative contribution of these perhaps transient immune-suppressive effects on the resistance problem remains an open question; however, similar (albeit weaker) effects than those observed for the HIV–TB interaction (increased antibiotic consumption, increased pathogen loads, lower fitness thresholds) are likely to occur in other systems as well.

Antagonistic interactions: immune-mediated competition

Interaction with the immune system does not necessarily lead to synergistic interactions between coinfecting pathogens. If the two coinfecting species or strains are antigenically or immunologically similar enough, the immune response to one strain or species may suppress the other. Examples of this type of interaction include different strains of *Streptococcus pneumoniae* [24] and the interactions between strains of the rodent malaria parasite *Plasmodium chabaudi* [25]. In such cases, the immune system mediates ‘apparent competition’, that is, the abundances of two pathogens are inversely correlated, as is the case for classic competition. It is also possible for pathogens to induce immune responses to unrelated pathogens. For example, there is some evidence that *Helicobacter pylori,* which can be a commensal, induces antibacterial immune responses that can suppress coinfecting pathogens such as TB or *Vibrio cholerae* [26]. The impact on the evolution of resistance is likely to be complex and context-dependent, but in most cases such interactions should limit the evolution of resistance unless treatment clears the competing pathogen. In the latter case, we might expect increased selection for resistance since the total antagonistic pressure on the focal pathogen would be reduced, potentially leading to suboptimal drug dosage [8,27].

Resource modulation

Pathogens exploit a diverse array of host resources (e.g., cells, tissue, and metabolites). Their survival and growth depends on efficient acquisition of these resources, which can be either hindered or helped by coinfecting pathogens.

Synergistic interactions: resource cooperation or indirect support

The presence of a coinfection may assist the focal infection in its acquisition of resources. For example, many bacteria engage in mutualistic behaviors such as siderophore production, which assists the whole bacterial population in iron-scavenging behaviors [28] (although note that this behavior may decline with the spatial scale of competition [29]). Assistance provided by a coinfection may also be a byproduct of other processes. Several studies have suggested that upper respiratory tract viral infections predispose hosts to bacterial

respiratory infections, in part, by improving adherence of bacteria to epithelial cells or by exposing basement membrane proteins useful for bacterial binding for both human infections [30,31] and animal infections [32]. Alternatively, viral infections can facilitate bacterial ones by producing substrates beneficial to bacterial growth [33]. A secondary infection may also catalyze transition of a primarily commensal organism to a pathogenic state. For example, bacterial colonization and biofilm formation often require stringent downregulation of virulence factors in order to facilitate evasion of the host's immune system. Thus, colonizing bacteria rarely express virulence factors sufficient to promote invasion [34]. In the setting of a secondary viral infection, however, virus-induced pyrogenic cytokine secretion often results in a hyperthermic state that may induce biofilm dispersion and expression of bacterial virulence proteins, increasing the likelihood of invasion [35]. More generally, inasmuch as the coinfecting pathogen may increase the growth rate of the focal parasite, it may also assist spread of resistance mutations by facilitating replication and thus increase the risk of *de novo* mutations arising.

A key resource for invading pathogens is the available habitat. Many interactions can lead to one pathogen species creating habitat availability for another. Biofilm development by bacterial species colonizing a wound [36] is one such example. As above, by increasing the density of the focal pathogen, such mechanisms imply that coinfections can increase the spread of resistance. This effect is potentiated when biofilms protect the residing bacteria from antibiotic agents (e.g., by limiting drug penetration), which can lead to suboptimal focal drug availability, facilitating the evolution of resistance [37].

Competitive facilitation (i.e., the presence of a coinfecting strain increasing the biomass of the focal strain) is observed in certain rodent malaria strain pairs [38]. Some evidence of competitive facilitation of drug-resistant *Plasmodium falciparum* strains is also reported in women following intermittent preventive therapy during pregnancy (IPTp) in Tanzania [39]. Uncertainty remains as to whether the main mechanism behind these observations is immune- or resource-driven. The immune-mediated interaction may be present if cross-immunity is not fully overlapping: one strain could benefit from the focus of the immune system on the coinfecting strain [40]. The resource-modulation interaction may be present because different malaria strains can prefer red blood cells of different ages and therefore may provoke different levels of red blood cell production [41,42]. The presence of a strain that preferentially targets older red blood cells could stimulate production of younger red blood cells, which might benefit a competitor (competitive facilitation), although clearly the reverse (competitive suppression) is also a possibility. Again, increased abundance provides an opportunity for either the appearance of a *de novo* resistance mutation or the persistence of resistance mutations with lower fitness.

Finally, a special type of resource modulation exists for infections that use immune system cells as a resource. The presence of a coinfection may increase the abundance of target cells, and thus aid the focal infection. For example, the presence of malaria, TB, or HCV may stimulate the production of target cells for HIV or stimulate viral replication [7,43,44] and thereby potentially promote the evolution of resistance.

Antagonistic interactions: resource competition

A resistant mutant of a focal pathogen may pay a fitness cost in the presence of a coinfecting pathogen by being outcompeted in the acquisition of resources [45]. This process, termed exploitation competition, may reduce the resistant mutant's within-host growth rate, density, or persistence [46]. The mechanism may be mediated by the effect of the mutation on enzymes with biologically important functions, since these are generally the targets of drugs [47]. The magnitude of the effect is likely to depend on the degree of resource-niche overlap between the focal and coinfecting pathogens, or the fitness advantages and abundance of a mutant strain relative to conspecifics in the case of multistrain infection [48]. For example, two pathogens with very different target cells (e.g., epithelial cells versus erythrocytes) are unlikely to enter into exploitative competition. By contrast, two different strains of malaria parasites, both targeting red blood cells of similar age and type, may be in direct competition; further examples of direct competition are given in Box 1 [8,49]. This also illustrates that the degree of competition may vary over the time-course of an infection as key resources are depleted [42].

A consequence of resource competition is that vaccination or chemotherapy that controls the pathology but does not eliminate the focal pathogen may prevent entry or suppress replication of a coinfecting pathogen. In other words, a drug treatment regime that does not fully clear the drug-sensitive strain could be able to control the resistant strain. This principle has been demonstrated in rodent malaria infections [8]. Similarly, epidemiological and experimental evidence suggests that well-controlled *Eimeria* infection in chickens can reduce *Salmonella* due to the inflammatory and immune mucosal responses in the intestinal compartments shared by the pathogens (reviewed in [50]). These phenomena highlight the complexity of competitive interactions, and how resource and immune mechanisms can play intertwined roles in coinfection systems.

A range of *in vitro* studies have provided evidence for the operation of exploitation competition [49] – for example, drug-sensitive *M. tuberculosis* strains outcompeting rifampin-resistant mutants [51]. While these studies provide proof-of-concept for exploitation competition, extrapolating fitness costs from *in vitro* to *in vivo* may be problematic (e.g., [52]). Evidence of competition is harder to obtain *in vivo* because the impacts of immunity and competition may be hard to distinguish [53]. A solution is to use perturbations of immunity and explore the impact that this has on performance of single infections and coinfections [54]. This type of experiment has indicated, for example, poor competitive ability of colonizing resistant *Staphylococcus aureus* strains in the presence of a resident strain, attributable to localized resources available on a ‘first-come, first-served’ basis [54]. Reduction of focal pathogen fitness in the face of exploitation competition by coinfecting pathogens implies that aggressive chemotherapy [55], which eliminates competing strains, may facilitate the spread of resistance.

A variation on the theme of exploitation competition can emerge when the resource of the focal pathogen proves to be a component of the immune system downregulated by the coinfecting pathogen, rather than a direct resource for the latter. The net result is the same – the focal pathogen may have a lower replication rate as a result of the immune-modulatory

activity of the first (e.g., measles–HIV coinfection [56]). This would reduce the potential for the spread of resistance in the focal pathogen.

Concluding remarks

Current thinking in chemotherapy and resistance-management of infectious diseases usually focuses on one pathogen at a time. By contrast, the examples from recent research provided here demonstrate the importance of taking into account interactions between pathogens and with commensal species in the microflora. Coinfections can make the outcome of treatment decisions context-specific, implying that optimal treatment policies may depend on the abundance of other pathogen species or strains (either within the treated host or in the host population) as well as on drug-mediated interactions (Box 2). As we outline above, outcomes in terms of both pathogen abundance and resistance evolution will be mediated by the degree to which interactions are synergistic or antagonistic. The understanding of the mechanisms underlying these interactions remains limited, but it can have major applied consequences. For a particular set of mechanisms, the outcome might be highly predictable, given the identity or mode of the two pathogens (such as HIV coinfection reducing the ability of the immune system to fight off opportunistic infections). Alternatively, factors such as host immunity, order of pathogen arrival, or bacterial mode (e.g., commensal or pathogenic) could have major effects on the direction of the interaction, immediately multiplying the number of components that need to be understood before one can begin to delineate the outcomes of treatment decisions for either patient health or evolution of resistance. For example, there is evidence that *H. pylori* coinfection can both help and hinder cholera coinfection in its pathogenic and commensal modes, respectively [26]. This is further complicated by the potential for complex nonlinear outcomes inherent in infectious disease dynamics, which might even lead to changing directions of outcomes over the course of an infection at the individual scale – and unpredictable links between coinfection at the individual scale and pathogen coexistence at the population scale [57].

One key challenge is to predict population-level consequences from mechanistic interactions in individual hosts [58,59]; or, in the opposite direction, to interpret ecological patterns of co-occurrence as evidence for within-host mechanisms. An example for these challenges is provided by the HIV–TB interactions. Small epidemiological studies have shown strong local associations between HIV and drug-resistant TB (e.g., [60]), and have shown that small HIV-positive populations can support the spread of a low-fitness drug-resistant TB strain [61]. Interestingly, however, there is currently limited larger-scale ecological evidence for the association of HIV with multidrug-resistant TB [62] – perhaps due to HIV-stimulated reactivation of older, nonresistant TB strains, and population-level competitive disadvantage of drug-resistant TB strains evolving in HIV-positive individuals [63]. Additionally, sometimes within-host and population-level dynamics can be at odds when it comes to interventions: a recent study in African buffalo showed that anthelminthic treatment improved survival rates after bovine TB infection, but exacerbated TB transmission [57]. These examples highlight the nontrivial relation between mechanistic interactions in individual hosts and population-level signatures; ecological data provide an important piece of evidence for theimpact ofcoinfections, and hence future public health and ecological research efforts should be optimized for the interpretation of such data.

An important consequence of these uncertainties is that while it is clear that coinfection may necessitate coordination of treatment policies between pathogens, many important questions still remain unanswered for many pathogen combinations (Box 3). Coinfected individuals may be in worse health than those with single infections [64], and may also pose the biggest risk of transmission to others (as shown in buffalo [65] and mice [66]). By contrast, the chemotherapy in these patients may pose a higher risk for resistance mutations and propagation, and coinfected individuals may be ineligible for treatment because of their comorbidities [67].

Many other areas of biology also wrestle with issues of evolution of resistance in complex multispecies communities, in particular agricultural science and resistance in herbicide and insecticide deployment [68]. For instance, the source-sink dynamics of biological invasion of resistant weeds to neighboring fields is an agricultural example of the spread of resistance to untreated hosts, and the complexity of cross-scale resistance dynamics. Similar patterns of unintentional human-mediated selection occur, wherein efforts to encourage growth in crops can spill over and impact weed evolution and the structure of the crop-pest community [68]. Also, a similar debate on optimal herbicide treatment, low dose versus high dose, is being held in agriculture, having parallel foundation in resource competition between herbicide-resistant and herbicide-susceptible weeds [69]. There may be opportunities to exchange expertise between fields; indeed, agricultural systems may even provide an excellent economic model system to study rapid adaptive evolution in response to treatment [70].

To conclude, it seems clear that coinfection is likely to be an important modifier in the evolution of resistance. However, the degree to which coinfecting pathogens interact remains unclear in many cases; and even where we know that interactions are occurring, the mechanisms are often poorly defined. Improvements in laboratory technology (e.g., whole-genome sequencing) and bioinformatic analysis will facilitate the exploration of currently unknown quantities such as the prevalence of multistrain infection in various pathogens, and some mechanisms of resistance acquisition may become clear with further technical advances. The challenge then becomes translating knowledge of interactions into treatment options. An array of unconventional opportunities may emerge with better knowledge of the underlying mechanisms. For example, influenza and streptococcal infections interact in a way that is detrimental to human health, and the mode of their interaction suggests that mechanisms that repair the epithelial cell wall, and thus reduce the effect of previous influenza infection by preventing one mechanism of interaction, might enable the avoidance of spread of drug resistance. Fecal transplants present another unconventional opportunity: thus far, they seem to be very successful in treating some bacterial infections [71], and also, of most relevance here, they show promise for treatment of antibiotic-resistant infections [72]. Similarly, recent advances in tapping the potential of uncultured bacteria have led to the development of the antibiotic teixobactin, which shows promising refractoriness to resistance [73]. More classically, better treatment strategies may be suggested by this information; for example, for coinfections such as HIV–malaria, identifying the interaction mechanisms may inform improvements in treatment, such as guiding research toward an alternative for cotrimoxazole (CTX) that does not select for antimalarial resistance, or one that encompasses the function of CTX and IPTp (prophylactic treatment against malaria during pregnancy). Generally, understanding in which direction and by which mechanisms

pathogen communities evolve in response to antimicrobial therapy may be vital for both the design of pharmaceuticals and maximizing the efficacy of clinical measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Coinfection — for the purposes of this review, the term coinfection is used in a broad sense, covering all combinations of infection with more than one pathogen or strain. We consider coinfections with multiple strains of the same species as well as infections with multiple species of pathogen (following [48]). This includes simultaneous infection (two pathogens or strains transmitted together), superinfection (one pathogen or strain infects a host where another is already present), and sequential infection (one pathogen or strain infects after a previous infection has cleared, potentially leaving residual changes in the immune or resource landscape that would affect the second pathogen).

Emergence — the emergence of a resistance mutation within a pathogen is generally the result of a *de novo* mutation. For bacteria, other possibilities include acquisition from other strains or species present in the vicinity of the pathogen, that is, via horizontal gene transfer.

Fitness cost — frequently, mutations conferring some degree of resistance are associated with a fitness cost in terms of reduced pathogen within-host growth rate, which translates into a reduction in transmission of the resistant pathogen. Such costs are often mediated by competition with other coinfecting pathogens, via direct competition, or apparent competition mediated by the immune system. Even mutations that apparently have no cost, for example, mutations involved in conversion of efflux pumps, will be affected by the presence of susceptible strains, purely in the fraction of transmission dominated.

Focal pathogen	we use the term focal pathogen to mean the pathogen initially targeted for treatment. Often, but not always, this can mean the pathogen causing either more severe or more recognizable disease.
Spread	once a *de novo* resistance mutation has emerged, it must spread within the population. This requires both successful replication within a host, and then spread through the population via transmission to other hosts.

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Box 1. Direct interactions

Competition:

Most examples in this review involve indirect pathogen interactions via a third pathway. Pathogens, however, may also enter into direct, or interference competition [46] by actively synthesizing molecules that attack competitors. Examples include bacteriocins for bacterial species [76] (such as the serine protease Esp produced by *Staphylococcus epidermidis* competing with pathogenic *Staphylococcus aureus* in nasal cavities [77]); pyruvate in competing strains of trypanosomes [53]; the reactive oxygen species produced by *Enterobacter* bacteria that impede development of *Plasmodium falciparum* within mosquitoes [78]; and inhibition of adhesion to intestinal mucus glycoproteins between gut bacteria [79]. Such attacks may reduce the numbers of competitors but may also directly supply resources, as when *Pseudomonas aeruginosa* lyses *S. aureus* and exploits the resulting released iron [80]. Again, if drug-sensitive coinfecting pathogens directly attack drug-resistant mutants, aggressive chemotherapy against the pathogens will tend to amplify the growth rates of resistant mutants.

Horizontal gene transfer:

Pathogens can also directly interact through horizontal gene transfer (HGT), that is, the exchange of genetic material between different strains or species. HGT requires coinfection or co-colonization of the treated pathogen with commensal microflora. In the case of between-strain transfer, resistance genes can be transferred from a resistant strain to a previously sensitive strain. This can increase the speed with which resistance mutations spread, facilitate multidrug resistance, increase the pool of resistance genes or mutations, and provide a reservoir for persistence of resistance genes.

Conversely, resistance mutations found at high densities in the microflora, coupled with HGT capacities of many key pathogens, suggest that the commensal microflora could be an important source and sink of resistance [81–85].

This implies that the control of a pathogen does not necessarily lead to control of resistance. However, the impact of the complexities (e.g., plasmid transfer dynamics [86–93]) of cross-species resistance transfer is understudied.

Box 2. Drug-mediated interactions

Drug-mediated complications in treating coinfected patients can affect the evolution of resistance in various ways. Here we focus on collateral selection of resistance linked to nontarget pathogens.

Collateral selection occurs when treatment of a focal infection selects for resistance in other pathogens or commensal colonizers. This occurs either because a competitor is removed or because the selective pressure promotes *de novo* resistance in the coinfecting pathogen. For many bacterial pathogens, collateral selection is a major mechanism of selection for resistance [84]. This is the case for several reasons. First, most bacterial pathogens typically colonize their host asymptomatically (e.g., *Staphylococcus aureus* and *Streptococcus pneumoniae*). Accordingly, symptomatic infections play only a small role in pathogen transmission, and treatment targeted at symptomatic coinfecting pathogens causes only a relatively weak selective pressure for resistance evolution in the focal pathogen. Second, many antibiotics (especially broad-spectrum drugs) are prescribed for many conditions and inhibit the growth of various pathogens. Antimicrobials reaching lethal concentrations for the target pathogen may be less lethal or only bacteriostatic for other bacteria, allowing the latter to acquire resistance. For instance, antimicrobial treatments can increase resistance in enteric bacteria, as antimicrobial concentrations in the intestine differ from those in the target organ [94], and the enteric bacteria can differ from the pathogen in drug susceptibility. Third, resistance genes can be genetically linked [95], and hence hitchhiking can increase resistance. Lastly, some bacteria (especially those capable of forming biofilms) are able to reduce antibiotic concentrations both intracellularly and across the biofilm, for example, through reduced outer membrane permeability [96], or indirectly through inflammation [97]: inflammatory fluids have low pH, and some antibiotics are less active in acidic conditions. Reducing drug concentrations can facilitate resistance evolution in both the focal pathogen and collateral selection for resistance in any other local infection.

One viral example of a collateral effect is the tenofovir-mediated HIV–hepatitis B virus (HBV) interaction [98]. Tenofovir is effective in treating both viruses and is often used as part of triple-antiretroviral therapy for HIV. This is often unproblematic and helpful for treating both infections. However, the other drugs in this combination are less (or not at all) effective against HBV, so combination therapy for HIV may only be monotherapy for HBV. Such a suboptimal genetic barrier for HBV may eventually select for HBV resistance rather than curbing HBV infection.

A similar example comes from HIV–malaria coinfection. Daily prophylaxis with cotrimoxazole (CTX) is recommended for HIV-infected patients to prevent opportunistic infections. As the drug acts on the same pathway as the antimalarial sulfadoxine–pyrimethamine (SP), daily CTX treatment selects for SP-resistant parasites[6,7]. Moreover, pharmacokinetic interactions between antiretroviral therapy and combination-based antimalarial drugs are reason for concern since these interactions can cause either increased or decreased drug bioavailability of antimalarial effect, thereby potentially increasing the risk of selection for drug resistance (reviewed in [99]).

Box 3. Outstanding questions

- How can we predict population-level consequences from mechanistic interactions at the within-host level?
- What is the optimal order of treatment of coinfecting pathogens?
- Should treatment be intensified in the presence of an immunosuppressive coinfection to compensate for the impaired killing by the immune system? What consequence does this have for resistance evolution?
- Should research and development of new drugs be focused on treatment of specific very common coinfections?
- At the population scale, should coinfected individuals be prioritized for treatment when there are limited resources?

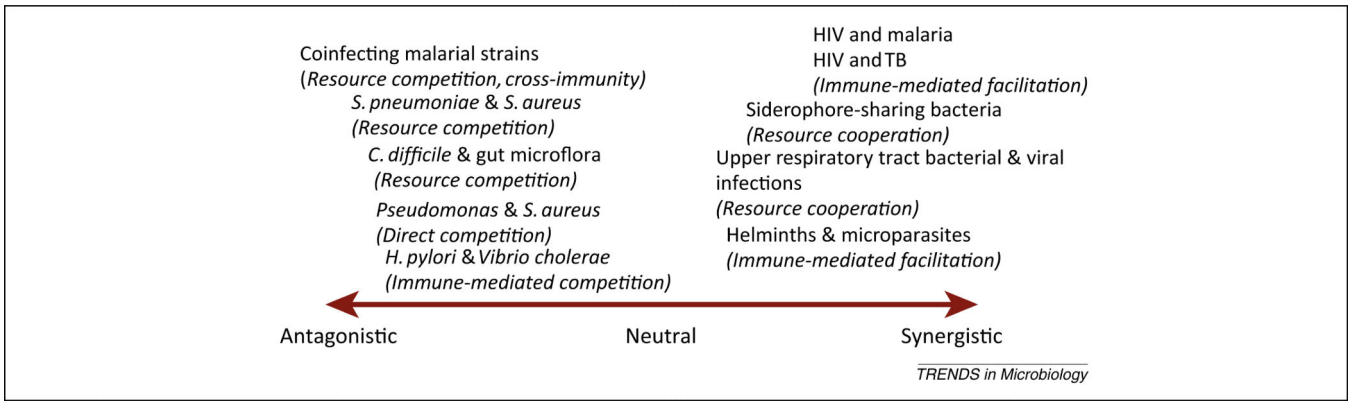

Figure 1.

Antagonistic to synergistic coinfections. Coinfection can have effects on focal pathogen density and replication. Different interactions, ranging from antagonistic to synergistic, can then have differing effects on chemotherapy and resistance. Species referred to in the figure: Streptococcus pneumoniae, Staphylococcus aureus, Clostridium difficile, Pseudomonas sp., *Helicobacter pylori* and *Vibrio cholerae.* Abbreviation: TB, *Mycobacterium tuberculosis*.

Table 1

Interactions at the scale of the individual[a]

	Beneficial	Neutral	1 Detrimental
Beneficial	HIV–HCV[b] [4]	Helminths beneficial for bacteria/viruses [17,18]	Cheating/cooperation in siderophore-sharing bacteria [28,29]
	HIV–TB[c] [3]		HIV–GB virus C[d] (detrimental to HIV) [74]
Neutral	–	Non-overlapping: *tinea pedis,* influenza	Fever-promoting: malaria detrimental for syphilis[75], *Helicobacter pylori* restricting (detrimental for) TB infection [26]
Detrimental	–	–	Competing strains: malaria (depending on strains) [38]

[a]Row labels correspond to the impact on one pathogen of the coinfection, while column labels correspond to the impact of the coinfection on the other.

[b]Hepatitis C virus.

[c]Mycobacterium tuberculosis.

[d]Formerly known as Hepatitis G virus or HGV.