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Biological control of emerging forest diseases: How can we move from dreams to reality?

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ABSTRACT

Biological control (BC) is defined as the use of living natural enemies, antagonists, or competitors (biological control agents) to control other living organisms. In the second half of the last century, the general interest in BC has increased considerably because greater environmental awareness in society and the implementation of integrated pest management (IPM) strategies have pushed towards the development of environmentally friendly control approaches. However, BC is still only rarely used for pathogens (fungi, bacteria, viruses, nematodes, and phytoplasmas) of forest trees. Here, we present and discuss the biological specificities of both the hosts and the fungal pathogens which may account for this situation. To increase the likelihood of BC success, we suggest a holistic approach involving the use of top-down regulators, competitors and amensalists, all exerting pressure on the pathogen, as well as bottom-up forces helping the host (e.g., endophytes, mycorrhiza). Moreover, BC to mitigate emerging forest diseases should be fully integrated into other sustainable management strategies. Finally, we propose guidelines for developing an efficient BC of emerging fungal pathogens of forest trees.

1. Introduction

In natural forests (i.e. forests which have reproduced naturally, consisting of naturally immigrant or indigenous tree species and strains; NFS, 2014), pathogenic organisms are key components of the ecosystem, playing a crucial role in the regulation of plant species diversity and distribution (Castello et al., 1995). However, over the last century, emerging diseases have increasingly been reported in both natural and artificial forests all around the world (Stenlid et al., 2011; Ghelardini et al., 2017). Examples of devastating emerging diseases include, in order of their first official report, chestnut ink disease (*Phytophthora cinnamomi* and *P.* × *cambivora*), chestnut blight (*Cryphonectria parasitica*), Dutch elm disease (*Ophiostoma ulmi* and *O. novo-ulmi*), sudden oak death (*Phytophthora ramorum*), pine wilt disease (*Bursaphelenchus xylophilus*), ash dieback (*Hymenoscyphus fraxineus*), and laurel wilt (*Raffaelea lauricola*) (Brasier, 2001; Futai, 2013; Harrington et al., 2008; Grünwald et al., 2012; Gross et al., 2014; Rigling and Prospero, 2018; Vettraino et al., 2005; Vieira and Mota, 2008).

Emerging diseases are recognized more and more by the scientific community as the component of global changes representing the main current and future threat to forest ecosystems (Fisher et al., 2016; Santini and Battisti, 2019; Thakur et al., 2019). As long as globalization and international trade intensify, the unintentional movement of species, including pathogens, will continue to increase (Westphal et al., 2008; Santini et al., 2013). These non-native (exotic, alien) introduced pathogens establish themselves easily in new areas where they encounter naïve hosts, with no or few natural enemies and competitors (Mack et al., 2000). Another cause of emerging diseases is climate change (Anderson et al. 2004). Gradual changes in climate, as well as climatic extremes such as drought, heat waves, hail, flooding, and frost, may alter host-pathogen interactions, thereby promoting diseases caused by native or non-native pathogens or by previously harmless organisms (Desprez-Loustau et al., 2007). For instance, widespread endophytic fungi of the family Botryosphaeriaceae (Ascomycetes) can become pathogenic on stressed trees and cause a broad range of symptoms (e.g., bark cankers, blue stain, and dieback) (Slippers and Wingfield, 2007).

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The third cause of emerging diseases is forest management and changes in land use which may alter the virulence of native pathogenic and endophytic species. The degradation of forest ecosystems due to management intensification, high planting density and monoculture development may contribute to increasing forest vulnerability to both native and non-native pathogens (Ghelardini et al., 2016; Prospero and Cleary, 2017). A textbook example is the Fordlandia story, i.e. Henry Ford's failure to produce rubber from Hevea trees (*Hevea brasiliensis*) in the Amazon, due to the Southern American Leaf Blight caused by the endemic fungus *Microcyclus ulei* (Ascomycetes) that killed about 200,000 trees growing on a surface of 3200 ha; Lieberei et al., 1989; Lieberei, 2007). Emerging diseases caused by native pathogens may also be enhanced by host-related factors such as a narrow genetic background. Large scale monocultures of genetically similar or identical (clones) non-native trees may be highly susceptible not only to invasive pathogens, but also to native pathogens that have experienced a host shift. In Southern Africa, for example, the native fungus *Chrysoporthe austroafricana*, an endophyte on native Myrtales, has shifted to the *Eucalyptus* species causing severe damage (Wingfield et al., 2008a).

Despite their increasing occurrence and significance, emerging pathogens in forest ecosystems are still particularly difficult to control because of the specificities of both the hosts and the pathogens. Unlike most agricultural crops, which are annual (e.g., wheat, potatoes), tree generations extend over several decades. Thus, control strategies need to be effective for many years, not only during a specific growing season (e.g., tillage or delayed seeding in annual crops, Cox et al., 2005). In plantations, the long lifetime of trees and the high economic costs do not always permit a regular switch (e.g., crop rotation) in the cultivated species. Fungi (in a broad sense, including oomycetes) are the most frequent pathogens in forests (Fig. 1) and are often characterized by complex life cycles. Fungal pathogens affecting the woody parts of trees (roots, stems, branches) usually persist for years in their host or in the rhizosphere (e.g. *Armillaria* species; Heinzelmann et al., 2019). Leaf fungi (e.g., rust or powdery mildew fungi), which have to re-infect leaves every year, may only persist in dormant buds, fallen leaves, and litter. To date, control of forest tree pathogens is mostly attempted through cultural practices and, at least in commercial plantations, by using resistant plant material (Woodcock et al., 2018). Hence, common measures to reduce the impact of fungal diseases include the use of locally adapted and resistant tree species, a mixture of different tree species, or the reduction of tree density (Prospero and Cleary, 2017). Direct chemical control of forest fungal pathogens has been widely applied in nurseries where impact of seedling diseases can be extremely high (Laatikainen and Heinonen-Tanski, 2002; Poteri et al., 2005). In forests, the use of fungicides is less common. In Western Australia, application of systemic phosphite (i.e. salts of phosphonic acid H_3PO_3) fungicides by stem injection or aerial spraying has proven to be effective in slowing the progress of the root pathogen *P. cinnamomi* (e.g. Hardy et al., 2001; Shearer and Fairman, 2007). Although this does not seem to apply to phosphite, a major issue of using fungicides on a landscape scale is the risk that they may also affect non-target beneficial organisms or cause problems for human health. Last but not least, repeated application of fungicides may promote the emergence of resistant genotypes in the target pathogen. For these reasons, chemical control is only available and authorized for a limited number of pathogens (e.g. powdery mildews in nurseries; O'Neill, 2020) and fungicides to control fungal pathogens in forests have been progressively banned by an increasing number of authorities, at least in Europe. Consequently, there is a tremendous demand for alternative control methods against tree pathogens.

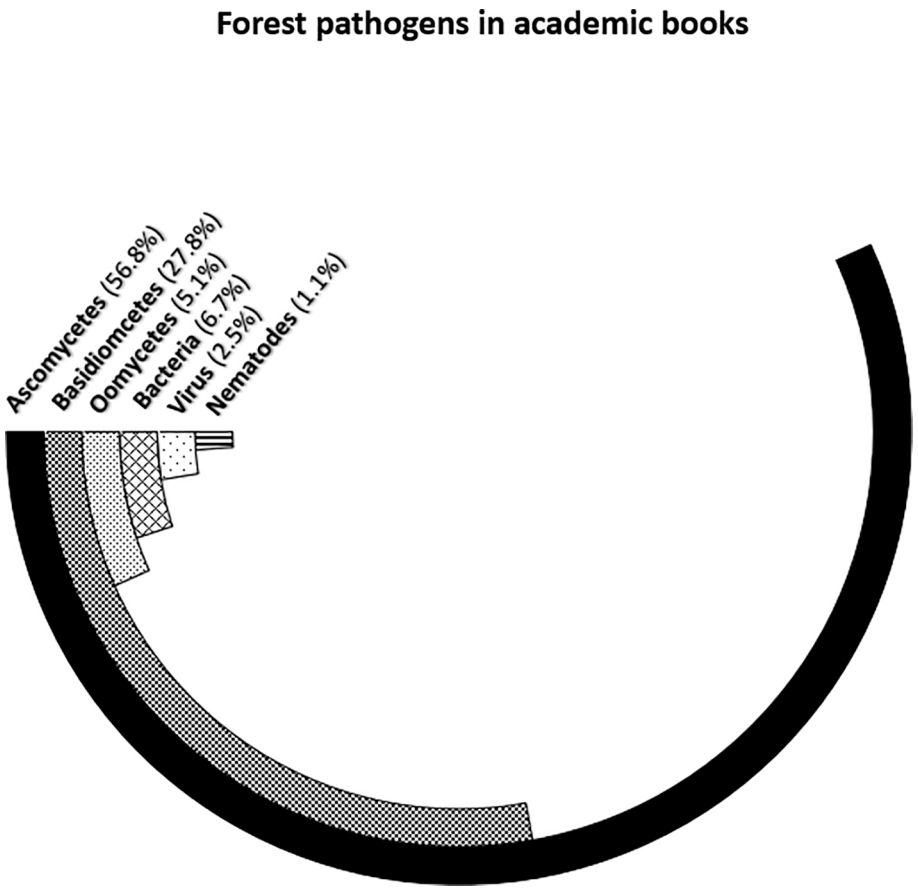


Fig. 1. Major taxonomic groups of forest pathogens causing tree diseases (according to Butin, 1995; Capretti and Ragazzi, 2010; Manion, 1991; Tainter and Baker, 1996). About 90% of the diseases are due to an infection by fungi in a broad sense (i.e. including oomycetes).

In a broad sense, biological control (BC) is defined as the use of living beneficial organisms (biological control agents, BCA) to control the pests (pathogenic agents or herbivorous insects) (Kenis et al., 2019). The main goal of BC is to achieve a self-sustainable and effective control of a pest by maintaining its population below acceptable thresholds. Among the three different BC approaches that have emerged, classical BC refers to "the introduction of a natural enemy of non-native origin to control a pest, usually also non-native, with the aim of establishing a population of the natural enemy sufficient to achieve the sustainable control of the target pest" (Kenis et al., 2019). By contrast, augmentation BC consists in regularly releasing exotic BCA which, in their new ecosystem, cannot establish sufficiently large populations to mitigate the pest's negative effect. Finally, conservation BC relies on natural enemies of pests which are favored through habitat manipulation (van Lenteren, 2012; Tsegaye et al., 2018; Kenis et al., 2019).

Classical BC has been developed mainly for managing non-native insect pests affecting agricultural crops (Cruttwell McFadyen, 1998; Van Driesche et al., 2010; Kenis et al., 2017; Schwarzländer et al., 2018; Barratt et al., 2018). In the classical BC approach, natural enemies are parasitoids or predators of herbivorous insects. They exert a top-down regulation on plant consumers, which are also submitted to bottom-up forces exerted by the plant (Showalter et al., 2018). A trophic web can thus be drawn between the plant (the first level), the herbivorous insects (the second level) which feed on the plant, and the predators (the third trophic level) which feed on the insects. A recent meta-analysis showed that in plant-insect trophic webs top-down forces are stronger than bottom-up forces (Vidal and Murphy, 2018), which may explain the success of classical BC strategies for managing non-native forest pests.

Although fungi are the main cause of emerging forest diseases, classical and augmentation BC are still poorly applied to mitigate diseases caused by these organisms compared to insect pests. The same holds true for conservation BC, whose concepts and limitations mainly apply to herbivorous insects in agriculture (Gurr et al., 2017). In this review, we aim at critically exploring and reframing the concept of BC applied to pathogens of trees. We focus on the most important guild: the fungi (in a broad sense, i.e. including oomycetes). Specifically, we discuss the following points: (1) Is the top-down regulation of tree fungal pathogens effective enough to allow BC strategies to rely on it? (2) Do non-native fungal pathogens require different BC approaches compared to native pathogens? (3) What are the limits and constraints of BC of forest tree fungal pathogens? And (4) How can we develop an effective BC approach for these pathogens?

2. Top-down regulation of pathogens and other biological interactions

Top-down regulation of plant pathogens has been the subject of few studies targeting a limited number of pathogens (Parratt and Laine, 2016). Indeed, plant pathosystems are not usually studied as trophic webs, and pathogens are generally overlooked in these food webs, in which they should actually be included as plant or animal consumers (Lafferty et al., 2008). However, pathogens may host hyperparasites or be consumed by mycophagous organisms (predators). Hyperparasites, which like super predators (i.e. predators of predators), kill plant pathogens, provide a direct fitness benefit at the plant level and reduce disease incidence at the plant population level. Non-lethal hyperparasites which reduce the fitness of their pathogenic host without killing them, contribute to decrease inoculum pressure and, consequently, disease severity and prevalence. Thus, both lethal and non-lethal hyperparasites are promising BCA candidates (Fig. 2). An example of a

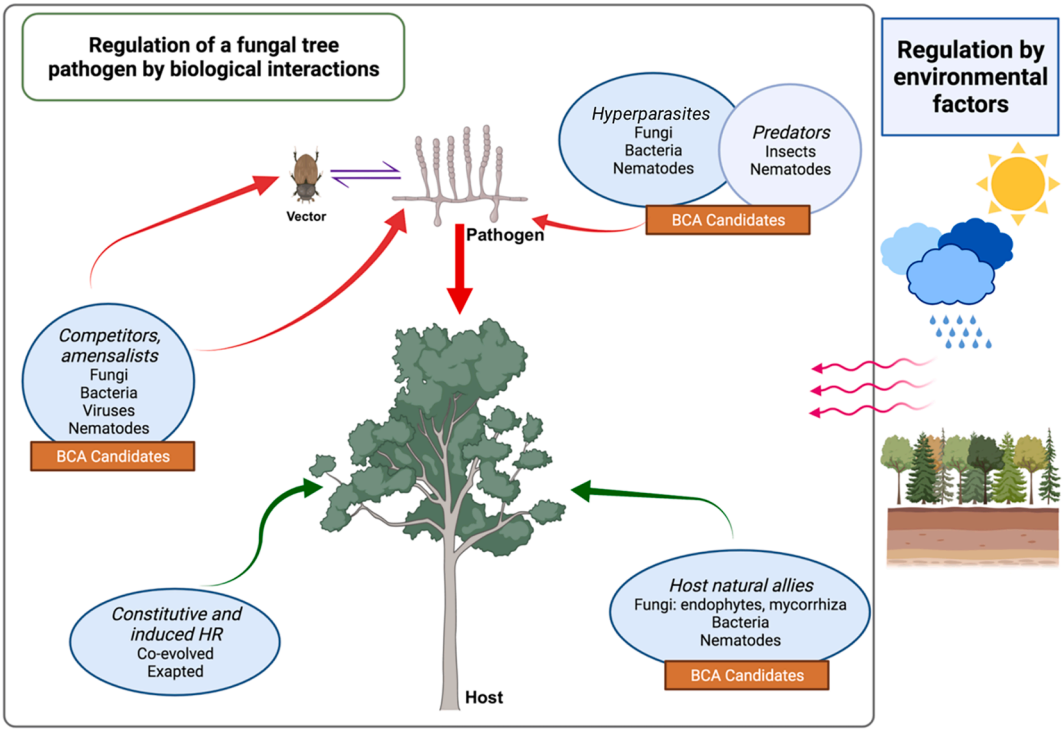


Fig. 2. Main factors of regulation of fungal pathogen (including oomycetes) - tree interaction and BCA candidates. The outcome of a tree-pathogen interaction is affected by hyperparasites and predators (top-down regulators) that negatively affect the fitness of the pathogen (eventually kill it) in presence of a trophic interaction with it, competitors and amensalists that negatively affect the fitness of the pathogen or its vector without a direct trophic interaction, host natural allies and constitutive and induced host resistance HR (both bottom-up forces) that help the tree against the pathogen. All interactions and effects are modulated by environmental factors that act (purple wave arrows) on the pathosystem (represented as box). BCA candidates may be searched among hyperparasites, predators, competitors, amensalists and host natural allies. Green arrows indicate beneficial effects to the host provided by constitutive and induced resistance, and natural allies. Red arrows indicate negative effects exerted by the pathogen to the host tree, by hyperparasites and predators to the pathogen, and by competitors and amensalists to the pathogen and its vector. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

successful non-lethal hyperparasite is the mycovirus CHV1 that reduces the fitness of the chestnut blight fungus *C. parasitica* without killing it (see Box 1). On the other hand, *Ampelomices* spp. are lethal intracellular parasites that suppress the sporulation of powdery mildew fungi and kill the parasitized fungal cells (Kiss, 2003).

According to the enemy release hypothesis (Mitchell and Power, 2003), hyperparasites should be more frequent in the native range of their hosts than elsewhere (Roderick and Navajas, 2003). Unfortunately, about 40% of all introduced forest fungal pathogens are of unknown geographic origin (Santini et al., 2013). Emblematic examples of such "homeless" pathogens are *Ophiostoma ulmi* and *Ophiostoma novo-ulmi* (Brasier and Buck, 2001), the two causal agents of Dutch elm disease (DED). In other cases, the center of origin is debated (e.g., *Bretzellia fagacearum*, the causal agent of oak wilt, Juzwik et al., 2008) or has only recently been identified (e.g., *P. ramorum*, Jung et al., 2021). This makes the finding of a hyperparasite in the native range of a pathogen very difficult, if not impossible. Some hyperparasites (e.g., mycoviruses) are so intimately linked to their pathogenic hosts that they may be introduced with them (e.g., hypoviruses of *C. parasitica* (see Box 1) or the d-factors in DED, Webber, 1993). However, multiple pathogen introduction routes (e.g., *C. parasitica*; Dutech et al., 2012), do not necessarily mean that hyperparasites are also introduced several times (Feau et al., 2014).

Although not frequently observed, non-coevolved hyperparasites may jump between hosts, and non-native pathogens may be parasitized by native hyperparasites. For example, the ubiquitous genus *Trichoderma,* which is trophically linked to several pathogens, may be a BCA candidate for non-native pathogens (see Box 2; Harman et al., 2004). Mycoparasitism of powdery mildew agents and other pathogens is also achieved by several different species, including *Ampelomyces* (Kiss, 2003).

During their whole life cycles, tree fungal pathogens are involved in other antagonistic biological interactions than producer–consumer interactions (Heydari and Pessarakli, 2010). Hence, BCA candidates can also be found among organisms that even in the absence of a trophic interaction with a tree pathogen, may have a negative effect on its fitness (i.e. antagonists; Schulz et al., 2019). Such interaction, called amensalism, can happen through antibiosis (i.e., the production of microbial toxins) and metabolite production (e.g., lytic enzymes). It can occur before the pathogen has attacked the tree host, as it is observed in suppressive soils. In this case, disease suppression may also result from the destruction of the inoculum through hyperparasitism (Adams, 1990). However, increasing evidence suggests that volatile organic compounds (VOCs) produced by microbes in soil atmospheres can contribute to the suppression of plant-pathogenic soil fungi (de Boer et al., 2019). Plants may also produce root exudates which can inhibit root pathogens. D'Souza et al. (2005) assessed the potential of 15 native Western Australian legumes to biologically control *P. cinnamomi* and showed that four species of Acacia have the ability to reduce soil inoculum of this invasive pathogen. By contrast, in competitive interactions, i.e. when two species are in competition for nutritive resources, both actors are harmed, even if one species may be more severely affected by a negative outcome and being excluded. As shown by Oliva et al. (2021) for *Diplodia sapinea* on pines, latent pathogens may compete with functionally similar endophytes for key metabolites, which may prevent the development of symptoms. Tree pathogens may also benefit from positive interactions with other species, such as commensalism or mutualism. Many fungal pathogens are commensals of their vectors (example DED fungi) or mutualistic (example ambrosia fungi in close relationship with ambrosia beetles). Hence, BCA candidates for such pathogens may be found among the natural enemies of these insects. For example, the presence of the fungus *Phomopsis oblonga* in the bark of *Ulmus glabra* was associated with the disruption of breeding of scolytid beetles which are vectors of *O. ulmi*, one of the causal agents of DED (Webber 1981).

3. Bottom-up regulation

Host resistance, including pathogen avoidance (e.g., by early flushing; Ghelardini and Santini, 2009) are bottom-up mechanisms that enable trees to escape or overcome the infection. Thus, all interactions that can stimulate the onset of defense mechanisms in the host contribute to these bottom-up forces. Enhanced resistance to pathogens may be conferred by the host's natural allies or the plant holobiont (see Box 3). For example, Martínez-Arias et al. (2019) showed that the endophytic mycobiome of *Populus alba* may reinforce the host's tolerance to *Venturia tremulae*, the causal agent of shoot dieback on poplars. Similarly, the microbial community present in suppressive soils or composts may enhance trees' growth and health (Bonanomi et al., 2018). Other studies have revealed that mycorrhiza protect host plants not only by improving nutrition, but also by preventing pathogen penetration (e.g., Branzanti et al., 1999) or by triggering defense responses (e.g., Jung et al., 2012). Since plants (including trees) are able to develop an immunological memory (so-called defense priming),

Box 1
Classical BC of chestnut blight, a top-down BC based on parasitism

Cryphonectria parasitica (Murr.) Barr., the causal agent of chestnut blight, induces perennial necrotic lesions (so-called cankers) on the bark of stems and branches of susceptible host trees (particularly *Castanea* species), eventually leading to the death of the plant part distal to the infection (Rigling and Prospero, 2018). This ascomycete is native to East Asia, where it occurs without causing significant damage to native chestnut species. In the 20th century, the pathogen was accidentally introduced into North America and Europe, where it encountered the susceptible host species *Castanea dentata* and *Castanea sativa*, respectively (Dutech et al., 2012). In North America, this resulted in a dramatic epidemic which caused the ecological extinction of the American chestnut (Elliott and Swank, 2008). In Europe, following an initial phase of high mortality, chestnut stands started to recover thanks to the appearance of non-lethal, superficial bark cankers (Heiniger and Rigling, 1994). Such cankers are caused by *C. parasitica* strains infected by the *Cryphonectria hypovirus 1* (CHV1), a positive-strand RNA virus that reduces the growth and sporulation capacity of its fungal host (causing so-called hypovirulence), thereby acting as a biocontrol agent against chestnut blight. CHV1, which also originates from East Asia, can be transmitted both vertically into asexual spores and horizontally via hyphal anastomosis between fungal strains belonging to the same vegetative compatibility group (VCG) (Rigling and Prospero, 2018). To date, natural hypovirulence occurs in most European chestnut growing areas. Where this is not the case, CHV1 can be artificially introduced into chestnut stands by treating bark cankers with a hypovirus-infected *C. parasitica* strain (Robin et al., 2010; Prospero and Rigling, 2016). Although therapeutic canker treatments are mostly successful, spontaneous spread of the artificially released hypovirus to untreated cankers is not always observed, calling into question the long-term success of this biocontrol method (Milgroom and Cortesi, 2004). In North America, biological control with CHV1 has nearly failed completely due to the high diversity of vegetative compatibility types in local *C. parasitica* populations, and the high susceptibility of *C. dentata* to the pathogen. Besides CHV1, *C. parasitica* hosts other fungal viruses, whose potential as biocontrol agents has not yet been completely investigated (e.g. Forgia et al., 2021).

Box 2
Trichoderma, a fungal genus widely used as top-down and bottom-up BCA in forest nurseries

The soilborne genus *Trichoderma* includes several species whose characteristics make them potential BCAs against plant and tree pathogens (Harman et al., 2004). Several strains and species of *Trichoderma*, such as *T. viride, T. harzianum, T. longibrachiatum, T. polysporum*, and *T. atroviride*, have already been successfully applied for the control of *Fusarium circinatum* in Chilean and New Zealand forest nurseries. For this, *Trichoderma* is produced by solid state fermentation (SSF) and inoculated into growing substrates and roots of *Pinus radiata* during the plant production process (Reglinski and Dick, 2005; Moraga-Suazo et al., 2011). Results have shown an improvement in the emergence and vitality of *P. radiata* seedlings when applied at the nursery stage. Likewise, inoculation of *P. radiata* seedlings with the *Trichoderma* species bio-inoculant Arbor-Guard™ improved the control of Armillaria root rot on pine. The pathogen appears to be inhibited at the transitory stage of seedling planting into plantations (Hill et al., 2010). Similarly, *Armillaria*-damaged oak seedlings treated with *T. virens* and *T. atrobrunneum* in Hungary were found to have better survival under harsh soil conditions than untreated controls (Chen et al., 2019). Recently, the combination of high-throughput DNA sequencing and host-symbiont network studies has revealed that different non-mycorrhizal fungi, such as *Trichoderma* spp. and other endophytes with broad host ranges, play a role in the interaction between arbuscular mycorrhizal (AM) and ectomycorrhizal (ECM) species in forest ecosystems (Toju and Sato, 2018; Oh et al., 2018). AM and ECM represent symbiotic associations between fungi and tree roots, which play a major role in the stability of the forest ecosystem and increase tree disease resistance and stress tolerance (Sinclair et al., 1982; Smith and Read, 2008; Summerbell, 2005). Furthermore, ECM colonization of seedlings in the nursery is important for the successful establishment and survival of young trees in the first years after planting (Perry et al., 1987). The outcome of the interaction between these three types of fungi (endophyte-AM-ECM) is yet to be clarified. Some studies have pointed out that because of its opportunistic and competitive behavior, *Trichoderma* spp. may negatively affect mycorrhizal colonization (Summerbell, 1987) but other investigations have shown that *Trichoderma* interacts positively with AM and ECM (De Jaeger et al., 2011). The possible application of *Trichoderma* spp. on adult trees has also been investigated, e.g. for the control of wood decay fungi (e.g. Schubert et al., 2008), but it seems to be more challenging than the use of these BCAs on seedlings in nurseries.

Box 3
Fungal endophytes as top-down and bottom-up forces

Fungal endophytes of trees are a group of ubiquitous highly-diverse fungi that live within host tissues without showing visible signs of their presence (Stone et al., 2004). They can be beneficial symbionts, dormant saprophytes, or latent pathogens (Saikkonen, 2007; Sieber, 2007; Slippers and Wingfield, 2007; Hyde and Soytong, 2008). To date, much is still unknown about the interactions of endophytes with plant hosts and other microorganisms (Zivanovic and Rodgers, 2018). However, with respect to the biological control of fungal pathogens, endophytes seem capable of acting both as top-down and bottom-up forces. On the one hand, they compete directly with pathogens for resources, and may be able to combat them by producing metabolites (e.g., peptides, steroids, phenols, terpenoids; Pavithra et al., 2020) that act as antimicrobials (Haggag, 2010; Terhonen et al., 2018). For example, Terhonen et al. (2016) showed that root endophytes of Norway spruce produce diverse kinds of metabolites with potential anti-fungal properties against various pathogens. Similarly, secondary metabolites produced by *Phialocephala europaea*, a dark septate fungal root endophyte of the *Phialocephala fortinii s.l. - Acephala applanata* species complex (PAC), have been shown to significantly inhibit the growth of *Phytophthora citricola in vitro* (Tellenbach et al., 2013). Besides affecting potential pathogens directly, endophytes may promote plant growth by producing phytohormones and providing nutrients to the host (Terhonen et al., 2018). An increasing number of studies show that fungal endophytes can supply host plants with phosphorus, potentially playing physiological roles similar to those of mycorrhizal fungi (Jumpponen, 2001; Almario et al., 2017). Furthermore, endophytes are known to stimulate plant-signaling pathways needed for plant pathogen resistance (Zivanovic and Rodgers, 2018). The inoculation of *Theobroma cacao* leaves with the foliar fungal endophyte *Colletotrichum tropicale* stimulated the expression of several host genes involved in the defense against pathogen and herbivore attack (Mejía et al., 2014). Raghavendra and Newcombe's (2013) inoculation study conducted on the leaves of *Populus* sp. suggested that leaf endophytes contribute significantly to quantitative resistance against Melampsora rust. Although the mechanism behind the mediation of host disease resistance by fungal endophytes is still unknown, treating trees that are susceptible to specific pathogens with endophytes that are known to improve pathogen resistance could represent an interesting option to enhance bottom-up forces.

increased protection against pests and pathogens may also result from a priming stimulus (Conrath et al., 2015). In this regard, Lehr et al. (2008) showed that inoculating roots of Norway spruce (*Picea abies*) seedlings with the soil bacteria *Streptomyces* spp. induced both local and systemic defense responses against the root rot fungus *Heterobasidion abietinum*. Similarly, the injection of healthy elm trees with the fungus *Verticillium albo-atrum* contained in the commercially available biological control product Dutch Trig® (Scheffer et al., 2008) enhances their resistance against DED (Postma and Goossen-van de Geijn, 2016). Endophytes (see Box 3) may successfully contribute to control fungal tree pathogens also by directly inhibiting pathogens via competitive exclusion or the production of antimicrobial compounds (Terhonen et al., 2018; Rabiey et al., 2019). For instance, Ulrich et al. (2020) analyzed bacterial communities inhabiting ash leaves and identified a set of isolates or phylogenetic groups that might be involved in preventing the penetration and spread of *H. fraxineus*, most likely either through direct antagonism or by inducing systemic resistance. Although bottom-up forces helping the tree may significantly contribute to the BC of pathogens, their effect is sometimes difficult to clearly assess in the field (e.g. mycorrhiza, endophytes) and may be influenced by changing environmental conditions (e.g., induced or primed resistance may be temperature dependent), by physiology and age of the host, by the pathogen growth and colonization, and may be host genotype dependent (Köhl et al., 2019).

4. Different biocontrol possibilities according to the host-pathogen association

The emergence of a disease requires the interaction of a virulent pathogen, a susceptible host, and a conductive environment (so-called disease triangle; Stevens, 1960). Hence, even if we do not always mention it, in each association the environment plays a key role in the outcome of the interaction and in the biological control. Here, we

characterize host-pathogen associations as they set the framework for the BC of fungal diseases. Based on the geographic origin of the pathogen, we consider two main associations: *i)* non-native pathogen × native/non-native host tree, and *ii)* native pathogen × native/non-native host tree (Table 1).

4.1. Biological control of non-native pathogens

New encounters between a pathogen and a host may result in severe disease epidemics. Indeed, non-native (i.e., non-coevolved with the tree host) pathogens may have negative consequences not only on native tree species, but also on non-coevolved non-native tree species grown in a specific area. Examples include *Phytophthora ramorum* on Japanese larch (*Larix kaempferi*) in the British islands (Brasier and Webber, 2010), *P. pini* on *Pinus radiata* in Chile (Durán et al., 2008), and *Fusarium circinatum* on *Pinus* species (mostly *P. radiata*) in plantations in the Northern and Southern hemisphere (Wingfield et al., 2008b).

Specialized and co-evolved hyperparasites are more likely to occur in the native range of the pathogen. In cases where such hyperparasites had accidentally been introduced with the pathogen (see CHV1 and chestnut blight, Box 1) or intentionally introduced and released after detection of the pathogen in the new area, their incidence can be further increased via augmentation BC. When classical BC is not possible, one may rely on the augmentation of generalist hyperparasites, which would have jumped to the introduced pathogen. Indeed, an outbreak of a newly introduced pathogen, becoming highly abundant, may drastically change the affected ecosystem. In this case, polyphagous organisms sharing the same habitat may switch to a different carbon source over time, adapting to exploit the newcomer as a main food provider (Gilbert and Parker, 2010). For example, Pepori et al. (2018) showed that the behavior of some species of the fungal genus *Geosmithia* associated with elm bark beetles has recently transformed into mycoparasitic behavior towards *Ophiostoma novo-ulmi*, one of the causal agents of DED.

Although several attempts have been made to biologically control some of the most devastating non-native pathogens with a top-down strategy, many potential BCA, although promising *in vitro*, have nearly completely failed in the field (e.g., for *Fusarium circinatum*; Martin-Garcia et al., 2019). Reasons for *in situ* failures include climatic constraints, the lack of alternative hosts, the development of resistance to the BCA, and biotic interference by native organisms (Schulz et al., 2019).

Enhancing bottom-up control forces by identifying natural tree allies

Table 1
Selected examples of pathogen × fungal host associations in forest ecosystems and currently known possibilities of top-down or bottom-up biological control.

Disease name	Pathogen* Host interaction * Geographic area	Pathogen origin	Interaction type (Pathogen × Host)[1]	Pathogen enemies or host allies	Pathogen regulation[2]	References
Chestnut blight	*Cryphonectria parasitica* × European Chestnut × Europe	Asia	NNat × Nat	*Cryphonectria hypovirus 1* (CHV1)	Hyperparasitism (TD)	Nuss (1992), Rigling et al. (2021)
				Bacillus subtilus	Antibiosis (AI)	Wilhelm et al. (1998)
Dutch elm disease	*Ophiostoma novo-ulmi* × European and American *Ulmus* sp. × Europe and North America	Asia	NNat × Nat	d-factor (mycovirus)	Hyperparasitism (TD)	Webber (1993)
				Geosmithia sp.	Hyperparasitism (TD)	Pepori et al. (2018)
				Phomopsis sp.	Antagonism (to the vector) (AI)	Webber (1981)
				Verticillium sp. (Dutch Trig$^{(R)}$)	Induction of tree defenses (BU)	Postma and Goossen-van de Geijn (2016)
				Fungal endophytes	Induction of tree defenses (BU)	Blumenstein et al. (2015)
Ash dieback	*Hymenoscyphus fraxineus* × *Fraxinus* sp. × Europe	Asia	NNat × Nat	Bacterial endophytes	Antagonism (AI)	Ulrich et al. (2020)
				Fungal endophytes	Antagonism (AI)	Kosawang et al. (2018)
				Hypoxylon rubiginosum	Antagonism (AI)	Halecker et al. (2020)
Phytophthora root rot	*Phytophthora lateralis* × *Chamaecyparis lawsoniana* × USA	Asia	NNat × Nat	*Enterobacter aerogenes*	Unclear	Utkhede et al. (1997)
Phytophthora root rot	*Phytophthora cinnamomi* × Multiple hosts × worldwide	Asia	NNat × Nat	Legume species	Antagonism (AI)	D'Souza et al. (2005)
Oak powdery mildew	*Erysiphe alphitoïdes* × *Quercus robur* × Europe	Asia	NNat × Nat	*Ampelomyces quisqualis*	Hyperparasitism (TD)	Kiss (2003)
Laurel wilt	*Raffaelea lauricola* × (Family Lauraceae) × USA	Asia	NNat × Nat	Entomopathogenic fungi	Antagonism (AI)	Danti et al. (2013)
Cypress canker disease	*Seiridium cardinale* × *Cupressus* sp. × Mediterranean area	Unknown	NNat × Nat	*Pseudomonas chlororaphis* subsp. *aureofaciens* (strain M71)	Antagonism (AI)	Raio et al. (2011)
				Trichoderma viride	Antagonism (AI)	Magro et al. (1984)
Kauri dieback	*Phytophthora agathicida* × *Agathis australis* × Oceania (New Zealand)	Asia	NNat? x Nat	Arbuscular mycorrhizal (AM) fungi, soil fungi and bacteria	Unclear	Padamsee et al. (2016), Byers et al. (2020)
Pitch canker	*Fusarium circinatum* × *Pinus radiata* × Europe and South America	North America	NNat × NNat	Endophytes	Antagonism and competition (AI)	Wingfield et al. (2008b), Martin-Garcia et al. (2019)
Scleroderris canker	*Gremmeniella abietina* × *Pinus halepensis* × Spain (Europe)	Northern Europe?	NNat × Nat	Endophytes	Antagonism (AI)	Romeralo et al. (2015a, b)
				Mycoviruses	Hyperparasitism (TD)	Botella et al. (2015, 2016)
Myrtle rust	*Austropuccinia psidii* × Eucalypts and other Myrtaceae	South America	Nat × NNat	*Fusarium decemcellulare*	Hyperparasitism (TD)	Amorim et al. (1993)
Diplodia canker	*Diplodia sapinea* × *Pinus* sp. × Europe	Europe	Nat × Nat	Endophytes	Competition (AI)	Oliva et al. (2021)
Heterobasidion root rot	*Heterobasidion annosum* s.l. × *Picea abies*, *Abies alba*, European *Pinus* sp. × Europe	Europe	Nat × Nat	Mycoviruses	Hyperparasitism (TD)	Kashif et al. (2019)
				Phlebiopsis gigantea	Competition (AI)	Korhonen et al. (1994)

[1] Nat = native, NNat = non-native.
[2] TD = top-down (trophic interaction), AI = antagonistic interactions (non-trophic), BU = bottom-up.

is especially appealing in the case of non-native pathogen × (native or non-native) host association, since intraspecific variation in host resistance is generally limited due to the absence of coevolution. Even if exapted resistance is present in natural populations of naïve tree species challenged by invasive pathogens (e.g., Hansen et al., 2000; Landolt et al., 2016; Bartholomé et al., 2020), its potential for use appears limited. The effect of tree allies on host defenses should be generalist enough to confer protection against pathogens that have not coevolved with the host. In a recent study, Halecker et al. (2020) identified an endophyte (*Hypoxylon rubiginosum*) inhabiting the leaves of European ash (*Fraxinus excelsior*) that produces metabolites which are toxic to the non-coevolved pathogen *Hymenoscyphus fraxineus*. Thus, this endophyte may have the potential to be developed into an effective BCA against ash dieback. In an inoculation experiment, Zampieri et al. (2017) showed that in *Pinus pinea* seedlings the presence of a native (*Heterobasidion annosum*) or a non-native (*H. irregulare*) root pathogen had the same enhancing effect on mycorrhizal density. However, the ectomycorrhizal symbiont (*Tuber borchii*) appeared capable of distinguishing the native from the non-native pathogen, probably through host plant-mediated signal transduction.

4.2. Biological control of native pathogens

When a native pathogen encounters a native, co-evolved host, the interaction rarely results in severe damage for the host. Indeed, in natural forests, native tree species generally have sufficient genetic variability or phenotypic plasticity to cope with native pathogens. However, drastic and rapid changes in environmental conditions could skew the balance in favor of the pathogen, with detrimental consequences for the host. *Diplodia sapinea*, the widespread and opportunistic agent of Sphaeropsis blight on conifers, which has been known in Europe since 1823 (Fries, 1823), can persist for long periods as an endophyte in asymptomatic tissues, becoming pathogenic as a consequence of drought stress (Stanosz et al., 2001; Santini et al., 2008). Human activity can also exacerbate environmental consequences, such as when trees are grown, even within their natural distribution range, on inappropriate sites. The incidence of native pathogens on native host trees can be increased by silvicultural practices as well. For example, in monospecific plantations of Scots pine (*Pinus sylvestris*) and Norway spruce (*Picea abies*) in northern Europe, after thinning operations, native *Heterobasidion annosum* s.l. spreads easily, colonizing the fresh stumps and penetrating neighboring trees through root anastomosis (Garbelotto and Gonthier, 2013).

Dramatic disease epidemics may result from new encounters between a native pathogen and a non-native host, typically in monospecific plantations. Planted forests generally represent very simplified ecosystems, more similar to an agricultural crop than to a natural forest. The genetic background of planted trees is usually narrow because plantations are generally issued from the progeny of a restricted number of genotypes showing superior growth and better wood quality characteristics (Paap et al., 2020). Plant species introduced to a non-native region experience a decrease in regulation by natural pests and pathogens (Colautti et al., 2004), resulting in a rapid increase in distribution and abundance. For this reason, plantations of non-native tree species have lived in a sort of ideal environment for long periods of time, without suffering the impact of pathogenic organisms. However, over the course of time, native pathogens, which are supposed to have a broad genetic basis, have frequently adapted to the introduced host trees that became new hosts. Such host jumps are relatively common among fungal pathogens, especially in those that have relatively broad host ranges (Woolhouse et al., 2005). For example, in southern Europe, the two native pathogens *Diplodia sapinea* and *Caliciopsis moriondi* are found on Douglas fir (*Pseudotsuga menziesii*) and Monterey pine (*Pinus radiata*), both of which are North American tree species (Botella et al., 2019; Migliorini et al., 2020). Another striking case is that of the myrtle rust fungus *Austropuccinia psidii* in South America. Starting in the 1970s, local eucalypt plantations have been increasingly attacked by this pathogen which, in South America, is endemic on native Myrtaceae (Coutinho et al., 1998).

Native pathogens may be controlled with local enemies whose incidence, if necessary, may be increased through conservation BC or augmentation BC. In the specific case mentioned above, *H. annosum* s.l. can be successfully controlled by applying a spore suspension of the fungus *Phlebiopsis gigantea* on the surface of fresh stumps (Korhonen et al., 1994) (see Box 4). This natural antagonist rapidly colonizes the stump, preventing the establishment of the pathogen. Bottom-up forces that help native trees should already be active (e.g., mycorrhiza, endophytes), but could be further enhanced artificially, for instance, by promoting accessory tree species that have a beneficial effect on the soil (e.g., *Alnus* spp. for nitrogen fixation). Even in the case of native pathogen × non-native host tree, augmentation and conservation BC could represent a meaningful and successful approach. Since the pathogen is in its natural range, we can imagine that at least a few of its natural enemies present sufficient genetic variability or phenotypic plasticity to cope with the new host tree. On the other hand, the possibility of using bottom-up forces to control the pathogen is most likely low, mainly because the host-pathogen interaction is new.

5. The pros and cons of BC for forest tree diseases

5.1. Narrow- or broad-spectrum BCAs

The complex life cycles of fungal pathogens and varied interactions with their hosts, make it extremely difficult to identify broad-spectrum BCAs. This is especially true for natural antagonists, acting as top-down BCAs and among them, for mycoviruses. Although all fungal taxa and oomycetes can host mycoviruses, the natural transmission of mycoviruses between unrelated host species is rare (Pearson et al., 2009; García-Pedrajas et al., 2019). The coevolution hypothesis, which states that mycoviruses have coevolved with their fungal hosts from an unknown but ancient origin, may account for this host specificity (Ghabrial, 1998). The same specificity is frequently observed in hyperparasites of biotrophic fungi. For example, Lutz et al. (2004) identified two lineages of *Tuberculina maxima*, a mitosporic parasite of rust fungi: one lineage was specific to *Gymnosporangium* species, whereas the other to *Cronartium* species. Negative non-intentional side effects of narrow-spectrum BCAs on other microorganisms cannot be excluded but seem to be rather rare, thus reducing the environmental risks related to the use of such BCA. On the other hand, high host specificity might affect the effectiveness of a BCA via host counter-adaptation, lack of persistence in the absence of the host, and other ecological and evolutionary processes (Brodeur, 2012).

Broad-spectrum BCAs, which more often act by antibiosis or competition on the targeted pathogen, may negatively interact with non-target species and/or beneficial species. However, their ability to infect different hosts may allow them to persist in the environment even when the population density of the target host is low. This may be advantageous for the control of fungal pathogens experiencing strong fluctuations in their abundance (e.g. leaf colonizing fungi). Determining the host range and the ecological behavior of BCAs need detailed investigations in the laboratory and greenhouse. Only once these investigations have been carefully conducted, can the specific agent be eventually released in the field. It is indeed essential that antagonists competing with the pathogen for resources do not themselves become invasive in the new ecosystem (e.g., strongly limit resource accessibility for native beneficial microorganisms).

5.2. The influence of hyperparasites on pathogen virulence evolution

Although hyperparasites appear to be widespread in nature, their impact on ecology, and the evolution of pathogens and their effects throughout food webs are still not completely clear (Parratt and Laine,

Box 4
Phlebiopsis gigantea against *Heterobasidion annosum* s.l.: a top-down BC based on competition for resources

Phlebiopsis gigantea, a common wood-rotting basidiomycete, is successfully used as a BCA of Heterobasidion root rot caused by different members of the *Heterobasidion annosum* s.l. species complex (Holdenrieder and Greig, 1998; Berglund et al., 2005; Thor and Stenlid, 2005). Heterobasidion root rot is a major problem in conifer plantations where the pathogen colonizes freshly cut stumps (e.g., after thinning) by airborne basidiospores (Hsiang et al., 1989), and then progresses into the root system and infects adjacent trees through root anastomoses (Asiegbu et al., 2005). Although resource competition has been noted as the most probable biocontrol mechanism of *P. gigantea* against *H. annosum* s.l. (Hodges, 1964; Holdenrieder and Greig, 1998), several biological features of this fungus seem to be relevant for its biocontrol action. These include (i) its higher nutrient acquisition capability compared to *H. annosum* s.l. (Asiegbu et al., 2005; Adomas et al., 2006), (ii) its ability to antagonize hyphae of *H. annosum* s.l. by hyphal interference (penetration, granulation and vacuolation of the cytoplasm, and loss of opacity) (Ikediugwu et al., 1970; Ikediugwu, 1976), (iii) its fast colonization of stump wood, and (iv) its strong ability to produce a sufficient number of asexual spores in culture (Sun et al., 2009). Artificial inoculations of *P. gigantea* on pine (*Pinus* spp.) stumps have shown a significant decrease in Heterobasidion root rot in several studies in England (Rishbeth, 1963; Tubby et al., 2008) and in the southern United States (Hodges, 1964). *P. gigantea* also appears to be effective in colonizing spruce (*Picea* spp.) stumps (Rishbeth, 1963; Korhonen et al., 1994). Although *P. gigantea* is common in the environment, natural levels of inoculum were found to be too low and sporadic to effectively control *H. annosum* s.l. without artificial inoculation (Rishbeth, 1963). Nowadays, three distinct biological control products based on *P. gigantea,* which differ in the methods of production and the formulations, are available and are regularly used for stump treatment in Europe: PG Suspension in the UK, PG IBL in Poland, and Rotstop in Scandinavia (Pratt et al., 2000).

2016). In theory, a trade-off between transmission and host damage should drive the realized virulence of a hyperparasite-free pathogen towards an optimal evolutionary stable strategy (Alizon et al., 2009; Doumayrou et al., 2013). The presence of a hyperparasite may disturb this trend. To date, empirical data on how a hyperparasite effectively impacts the virulence of a fungal pathogen over the long-term is by and large lacking. On the one hand, when, for a given pathogen, low virulence is optimal for an evolutionary stable strategy, infection by a hypovirulence-inducing hyperparasite may be beneficial (Parratt and Laine, 2016). On the other hand, hypovirulence-inducing hyperparasites may also select for higher virulence in specific pathogens. Intraspecific differences in hyperparasite virulence and pathogen susceptibility to the hyperparasite may further affect the outcome of the interaction. For example, Bryner and Rigling (2012) experimentally showed that more virulent CHV1 strains, which strongly debilitated the chestnut blight fungus *C. parasitica*, had higher host-to-host transmissibility. Finally, as shown again for the chestnut blight pathosystem, the interaction pathogen-hyperparasite can also be strongly influenced by environmental conditions (Bryner and Rigling, 2011).

5.3. Registration and cost development

Similar to chemical pesticides, classical and augmentative BCAs need to be registered and authorized by the responsible authorities before being released in forests. This registration process, although necessary to avoid effects on non-target organisms, increases costs and the duration of development, and may prevent some private companies from investing in the proof-of-concept of a new method. For instance, in the European Union data requirements for the registration of BCAs in the current legislation go back to 2001, and even though the legislation was revised in 2009, the principles for evaluation and decision making remained the same, strictly following a precautionary principle (Köhl et al., 2019). Meanwhile, effective BCAs are urgently required by forest growers and managers who are trapped between the decreasing number of fungicides officially allowed and the lack of valid alternatives. Proposals for a balanced regulatory environment would lead to better access to BCAs and, thus, to further reductions in the use of fungicides (http://www.rebeca-net.de). The assumed risks of BCAs seem to be far from reality in the practice of BC (Koch et al., 2018; Lugtenberg, 2018). Several studies (e.g. Köhl et al., 2019) have questioned the ecological impact of BC assumed by authorities and proposed that the data requirements should be interpreted specifically depending on the origin of the BCAs (native vs. non-native).

6. Guidelines to develop biological management of tree pathogens

Based on the theoretical and practical points discussed in the previous sections, we suggest the following guidelines and recommendations for developing successful biological controls of fungal tree pathogens:

***1. Identify the causal agent of a disease*:** At first, the causal agent of a given disease must be unequivocally identified using standard sampling and diagnostic approaches. The frequent occurrence of species complexes (e.g. in the genera *Erysiphe* and *Fusarium*), the difficulties encountered in correctly identifying the fungal species responsible for a new disease (e.g., ash dieback) and the significant effect of other potential disease drivers (e.g., environmental factors) show to what extent the correct identification of the causal agent of a disease is not always trivial (Desprez-Loustau, et al., 2016). Furthermore, analyses must include establishing the causative relationship between the pathogen and the disease it produces (fulfillment of Koch's postulates).

***2. Identify the origin of the pathogen*:** Once the causal agent of the disease has been rigorously identified, if the pathogen is not native to the area where the disease has appeared, its geographic origin and introduction pathways should be determined. Genomics and bioinformatics provide new tools for such studies, as well as for biosurveillance and early detection of new diseases with sentinel plantings (Hamelin and Roe, 2019; Bergeron et al., 2019; Luchi et al., 2020; Morales-Rodríguez et al., 2019).

***3. Collation of data on host biology and ecology*:** To identify the constraints, outlooks and expectations of BC for a targeted pathosystem, the host(s) of the pathogen must be characterized in regard, e.g., of its life history traits (e.g. growth, dispersion, survival), the different biological interactions in which it is involved (biotic niche), the abiotic drivers of its distribution (abiotic niche) and, for timber tree species, silvicultural practices and production objectives. For this characterization, pathologists should collaborate with ecologists and foresters.

***4. Decipher the trophic web, the ecology of the pathogen, and the hosts*:** The aim of this step is to identify, for a targeted pathosystem, the BCA candidates, which may be top-down regulators (predators or hyperparasites), other antagonistic organisms of the pathogen or of its vector, as well as biotic agents which reinforce the bottom-up forces that help the host. This is particularly important when the pathogen is not native to the area where the disease is observed. Exhaustive studies of pathogen natural enemies in the geographic origin of the pathogen should guide our choice of BCA candidates for an effective top-down BC. Similarly, host natural allies (e.g., endophytes, mycorrhiza) that

enhance and promote tree health, are most likely to be found in the geographic origin of the pathogen. This knowledge is the prerequisite for the definition of the best strategy of BC to deploy. Three different options are available: according to the type of BCAs, we can decrease i) the inoculum quantity or pathogen population under a threshold, ii) the probability of tree infection by the pathogen or iii) the impact of pathogen growth within the host tissue (Cook, 1993).

5. Check the potential of BCA candidates and scale-up: The efficacy of the BCA candidate has to be initially assessed with *in vitro* and *in planta* tests. This allows us to answer biologically and ecologically relevant questions concerning the BCA, including its mechanism of action, host range (specific to the target pathogen or broad-spectrum?), dispersal ability, and the chances of successful establishment after introduction in the target area. To go further and scale-up, it is necessary to test potential formulations in forest trials.

6. Screen the best strains/genotypes/provenances of BCAs: These tests are necessary to choose which strains/genotypes/provenances of the studied BCA should be applied to control the target pathogen. Indeed, significant differences may exist in the outcome of the pathogen × BCA interaction (e.g., the different subtypes of CHV1; Robin et al., 2010) or specific strains/genotypes/provenances may perform better than others in the introduced range of the pathogen (e.g., because of different environmental conditions). For emerging diseases caused by native pathogens, such investigations can suggest which BCA should be facilitated or augmented.

7. Set up the BCA deployment strategy: Whatever the pathosystems and the BCAs are, their deployment should take evolutionary principles into consideration. Indeed, the success of BCA establishment in an introduced area depends on genetic and demographic parameters and on environmental factors (Fauvergue et al., 2012; Schoville et al., 2012). Knowledge of the main evolutionary processes that have shaped BCAs' ancestral populations is important to develop the best deployment strategy. For example, for fast evolving RNA mycoviruses, diversifying the origins of BCAs could prevent the failure of their establishment, as occurred with CHV1 in the USA (Feau et al., 2014).

***8. Develop complementarity of biological control*:** BC measures alone are often not effective enough to maintain populations of a pathogen below acceptable thresholds. This is especially true in forest ecosystems, where the outcome of the interaction between pathogen and BCA may be strongly affected by biotic and abiotic factors, which can themselves vary significantly on a small scale. Information regarding other potential disease drivers (e.g., changes in the environment or in native pathogen populations) is also necessary to mitigate this disease in an evolutionary and innovative approach (Desprez-Loustau et al., 2016). Thus, BC must be combined with other measures (e.g., sanitary cuttings to reduce inoculum sources, the use of more resistant trees or more diversified tree plantations) in an integrated disease management approach.

7. Conclusions

Although BC is a promising and environmentally-friendly approach for pest management, it is still only rarely adopted for forest pathogens where just a few successful cases are known. As highlighted in this paper, this could be due to several factors, including the biology and ecology of the involved actors (e.g., long generations of hosts, complex life cycles of pathogens, differences among strains/genotypes/provenances of the hyperparasite in their performance), the lengthy research requirements (e.g., from *in vitro* to *in planta* and *in situ* tests), and the regulation process which strictly follows a precautionary principle. Thus, more research is needed to identify and to introduce and spread new BCAs. To increase the chances of success of BC in forest pathology, we suggest a holistic approach, involving the use of top-down regulators, competitors and amensalists, all exerting pressure on the pathogen, as well as bottom-up forces helping the host. Moreover, BC for the purpose of mitigating emerging forest diseases should be fully integrated with other sustainable management strategies (e.g., sanitation cuttings, reduction of host density, and enhancing the use of resistant trees).

8. Glossary

Amensalism: a two-species interaction in which one species is harmed and the other is neither benefited or harmed (Kitching and Harmsen, 2018). Other species interactions mentioned in the paper include **Commensalism** (a two-species interaction in which one species benefits and the other is neither benefited or harmed; Mathis and Bronstein, 2020) and **Mutualism** (a two-species interaction in which both species benefit from the relationship; Bronstein, 1994).

Avoidance: a mechanism of disease escape that occurs whenever susceptible plants do not become infected because the factors necessary for disease development do not coincide, interact at the proper time, or interact for a sufficient duration (Ghelardini and Santini, 2009).

Biological Control Agent (BCA): a natural enemy, antagonist or competitor, or other organism used for pest control (International Standard for Phytosanitary Measures (ISPM) 3; FAO, 2006)

Emerging disease: a disease caused by pathogens that (i) have increased in incidence, or geographical or host range; (ii) have changed pathogenesis; (iii) have newly evolved; or (iv) have been newly discovered or recognized (Anderson et al., 2004).

Parasite (and derived definitions): an organism whose life depends on another organism (the host). **Pathogen** refers to a parasite (most often, a microorganism) that infects and produces disease (a dysfunction which may lead to mortality) in its host. A **hyperparasite** is an organism which establishes a parasitic interaction with a parasite. In the case of a **mycoparasite,** this parasitic interaction occurs with a fungus.

Pathosystem: Strictly speaking, a host × pathogen interaction. In a broader sense, it encompasses the environmental factors associated with the host and the pathogen.

Resistance: the ability of an organism to exclude or overcome, completely or in part, the effect of a pathogen or other damaging factors. **Exapted resistance** is a form of resistance not favored by co-evolution with a pathogen, but evolved for other functions (Gould and Vrba, 1982)

Suppressive soil: soil in which a pathogen i) does not establish itself or persist, ii) establishes itself, but causes little or no damage to the host, or iii) establishes itself and causes disease for a limited period of time (Baker and Cook, 1974). General suppressiveness is attributed to the activity of the soil-inhabiting microbiome, and is often associated with competition for resources, whereas specific suppressiveness is the result of the activities of specific groups of microorganisms that interfere with some stage of the life cycle of the pathogen (Gomez Expósito et al., 2017).

Susceptibility: the inability of a plant to resist the effect of a pathogen or other damaging factors.

Tolerance: the ability of a plant to reduce or offset the fitness consequences of an infection by a pathogen without recovering from the infection.

Virulence (and derived definitions): for pathologists it quantifies a pathogen's capacity to damage its host and cause disease. **Hypovirulence** refers to the attenuation of the pathogen's virulence (Choi and Nuss, 1992).

Declaration of Competing Interest

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

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