



Darwinian black box selection for resistance to settled invasive *Varroa destructor* parasites in honey bees

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Abstract Established invasive species can pose a continuous threat to biodiversity and food security, thereby calling for sustainable mitigation. There is a consensus that the ubiquitous ecto-parasitic mite *Varroa destructor*, an invasive species from Asia, is the main biological threat to global apiculture with *Apis mellifera*. *V. destructor* has almost completely wiped out wild European honey bee (*Apis mellifera*) populations. The only remedy for apiculture, to date, is frequent control measures against the mite throughout the season, which prevents possible adaptations. While targeted breeding efforts have, so far, not

achieved the selection of tolerant or resistant bees, natural selection approaches have succeeded at least seven times. Here, we propose to take advantage of natural selection for honey bee resistance by stopping mite treatment in managed colonies. The main principles are within population mating of the colonies' own virgin queens and drones and selection based on survival and proliferous development of colonies. Being used for 10 years, it has shown to result in *grosso modo* 'normal' colonies with a high level of resistance to *V. destructor*. Here, we call for local groups of beekeepers and scientists to join a novel natural selection program that has started so far on three locations. This will eventually lead to several locally adapted *V. destructor* resistant honey bee populations around the world, and help global apiculture becoming more sustainable.

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Introduction

The Western honey bee (*Apis mellifera* L.) has an almost global distribution, both as wild (endemic in Europe, Africa and the middle-East, naturalized in the Americas, Asia and Australia) and as a managed

species (Moritz et al. 2005). *A. mellifera* is the most important managed pollinator species, thereby contributing to both food security and production of apicultural products worldwide (honey, pollen, wax and propolis, Klein et al. 2007; Aizen et al. 2008). It is therefore evident that apiculture is of significant economic and societal value.

As a consequence of the globalization of apiculture, the number of novel pathogens affecting *A. mellifera* has increased through host shifts from closely related species. This was the case for the ecto-parasitic mite *Varroa destructor* (Anderson and Trueman 2000), which has shifted hosts from the Eastern honey bee (*Apis cerana*) to *A. mellifera*. This mite has now an almost ubiquitous distribution (Ellis and Munn 2005) and is the primary biological cause of *A. mellifera* colony mortality worldwide (Neumann and Carreck 2010; Rosenkranz et al. 2010). *V. destructor* is a very efficient vector of several honey bee viruses, generating a disease epidemic within the colony, which dwindles until it dies within 2–3 years (Neumann et al. 2012).

The global spread of *V. destructor* has been very rapid, leaving very little time to mitigate against the biological invasion by preventing introduction, eradicating introduced mites, or finally, by inhibiting further spread (Van der Weijden et al. 2007). Interestingly, *A. mellifera* is the only honey bee that did not naturally carry parasitic brood mites before its exposure to *V. destructor* (Eickwort 1994). The apparent lack of host–parasite co-evolution history just after hosts shifts (Woolhouse et al. 2005), may explain the much higher susceptibility of *A. mellifera* towards *V. destructor* and, as a result, the rapid decline of wild and feral European (-derived) honey bee populations globally since the spread of *V. destructor* began (Rosenkranz et al. 2010; Villa et al. 2008; Kraus and Page 1995). Even though it is inevitable that natural selection would result in *A. mellifera* adapting to *V. destructor* if managed colonies were left untreated, this option was not considered in apiculture as the foreseen loss of colonies raised understandable concern over the sustainability of crop pollination and hence food security (Klein et al. 2007; Aizen et al. 2008). Therefore, *V. destructor* has been permanently controlled in managed colonies, preventing coevolution processes (as predicted by Oldroyd 1999), leading to host resistance and tolerance or lowered virulence

of the parasite, to take place (Neumann and Blacquière 2017; Brosi et al. 2017).

There is clear evidence that wild populations of *A. mellifera* can survive *V. destructor* infestations by means of natural selection (Seeley 2007; Le Conte et al. 2007; Fries et al. 2006; see Locke 2016 for a review). This also holds true for managed populations, which have not been treated against *V. destructor* (Oddie et al. 2017, 2018; Kruitwagen et al. 2017; Panziera et al. 2017; McMullan 2018). Therefore, sustainable beekeeping without the need to treat *V. destructor* is clearly feasible. Even though the mechanisms underpinning resistance to *V. destructor* infestation without treatment are not yet fully understood, we propose to take advantage of Darwinian natural selection for adaptation of bees to this novel parasite as an integrated part of local beekeeping practice. We present an outline for a (natural) selection route that can be incorporated in any local beekeeping, which includes methods to limit collateral damage, such as reinvasion in neighboring apiaries. The protocol [named ‘Darwin’s Black Bee Box’ (DBBB)] has been derived from 10 years of earlier work (see Panziera et al. 2017; Kruitwagen et al. 2017), and is going to be further tested in a new project that has just started at three locations (i.e. with three local groups of colonies). We here call for beekeepers and bee researchers to join this project and follow simultaneously the scheme outlined below at their own locations.

Darwin’s Black Bee Box

The scheme is based on the principles of evolution by natural selection: colonies able to survive and reproduce successfully pass on their genes to the next generation. Alleles of genes coding for traits contributing to survival will gradually increase in frequency, while harmful or neutral alleles will become less frequent. Like Darwin’s observations, it is possible to observe adaptations without understanding the underlying mechanisms. Here, we use the analogy of a black box from which the content remains hidden while the obvious effects of this content are nonetheless clear and visible. Moreover, the route does not beforehand qualify certain traits thought to be of advantage, but just follows nature to the outcome of survival and reproduction. Inside the black box, alleles

associated with a successful phenotype are conserved and will persist in the next generation. Natural selection is therefore ‘inclusive’ as it maintains genetic diversity by keeping all surviving phenotypes in the black box, including possibly rare alleles beneficial for resistance to parasites and pathogens (Delaplane et al. 2015). Targeted selective breeding programs, on the contrary, are by definition reducing genetic diversity by selecting from the surviving phenotypes only those of their preference of chosen traits, thereby potentially *excluding* many of the phenotypes despite their shown capability of survival (Uzunov et al. 2017). DBBB selection follows the natural seasonal reproduction cycle of honey bee colonies, mimicking swarming by splitting colonies. Consequently, the population not only preserves its genetic diversity, but also its associated diverse biome (both favourable and unfavourable associated organisms; bacteria, yeasts, fungi, viruses, mites, etc.) which fosters development of less virulent host–parasite relationships (Neumann and Blacquière 2017; Blacquière and Panziera 2018). This also precludes a next generation queen being confronted with a completely new biotic environment (colony plus biota). Vice versa it prevents colony offspring (plus biota) being exposed to a foreign young queen (queen + possible biota). Below we describe the practical principles and methods used in the approach, which we actively advocate to use wherever possible in a well-structured manner.

Preconditions

1. 25–30 colonies

The DBBB program can be started in spring with a population of 25–30 genetically diverse local colonies (from different beekeepers) from one region. This enables ample variation and conserves local/regional adaptation in the population (genotype–environment interactions Büchler et al. 2014). After splitting the successfully developing colonies into four nucleus colonies (see Procedure below), in the first year these colonies must be treated against *V. destructor* once, when the young queens have started laying eggs and prior to brood capping, by spraying with oxalic acid. The colonies that survive winter into the next spring, and which show good spring development (growth

of the colony and drone production), will be the parent colonies to produce the next generation. In mid-winter, when sampling bees for mite infestation occurs, a quarter of the nucleus colonies can be chosen to serve as a control group. The presence of a control/reference group of colonies is not necessary for the selection procedure, but it can be very helpful in order to compare the selected and non-selected groups in the future to reveal the local mechanisms enabling colony survival despite *V. destructor* infestations.

2. Remote area

A remote area is needed in the beginning of the summer to mate queens and drones within the population. If a control group of colonies is part of the set-up, a separate remote area will be required. We consider an area with no or hardly beekeeping in a radius of 3 km as being adequately isolated. The work of Jaffé et al. (2009) and Moritz et al. (2007) concluded that in a radius of 1200 m, 60–75% of the matings were with drones from within. In a trial of Jensen et al. (2005) the mating distance (flight radius of queens + flight radius of drones) was in 50% less than 2.5 km, and for 90% within 7.5 km. The higher latter distance can probably be explained by an increase in the flight range of queens, presumably caused by a lack of drones in the area (as reflected by a reduced number of matings per queen, Neumann et al. 1999a, b).

The DBBB selection scheme that we propose is based on negative selection (non-survival of non-adapted phenotypes) and does not aim for strong increases of specific (chosen) traits/phenotypes. Therefore, if a few foreign alleles enter the genepool this will probably not interfere with the natural selection process. Moreover, the DBBB procedure (see below) produces an excess of mature local own drones at the right mating time, which will most likely outcompete far flying foreigners by far.

3. No *Varroa destructor* control

No *V. destructor* control is applied to the DBBB selection colonies throughout the duration of the program, apart from the one oxalic acid treatment in the first summer. Conversely, *V. destructor* is controlled in the control group in order to keep the population of mites at an acceptable level to avoid damage and to avoid selection pressure by *V.*

destructor infestation taking place in control colonies too. In our case, the use of oxalic acid in the absence of capped brood twice a year proved to be a sufficient control treatment (Panziera et al. 2017).

4. Feeding of the colonies

Feeding colonies is obviously not natural. We know from the work of Seeley (1995, 2017) that in the wild (here Arnot Forest), only 23% of founder colonies from primary swarms that successfully occupy a nest cavity are able to survive the first winter. In the case of established colonies, the winter survival rate increases to 84% (Seeley 2017). Starvation over winter may be the prime cause for not surviving of colonies in the wild. In comparison, > 95% of well managed bee colonies (= well fed and treated against *V. destructor*) in Germany survive winter (Genersch et al. 2010). In our scheme, we avoid an extra selection pressure due to the lack of food by feeding the young colonies with sugar dough. In periods of poor forage, established colonies should also be fed.

5. Minimum duration of 4 years

The program should run for at least 4 years to see the first effects, and preferably be continued. The reason being that in a previous trial in the Netherlands we saw changes in *V. destructor* reproduction success in the non-treated colonies after 4 years (Panziera et al. 2017; Kruitwagen et al. 2017). Recent research of Avalos et al. (2017) showed that evolution by passage through a selective bottleneck can be very fast indeed (only ten generations/years) in the highly polyandrous honey bee.

Procedure and principles

No control of V. destructor: in the DBBB selected colonies, the control of *V. destructor* will be ceased after the first summer. Ultimately, only adaptation of the bees to the novel parasite is a vital option (possibly including mite adaptation, see Seeley 2007), every other being a dead end.

Reproductive capacity: in temperate regions, a wild *A. mellifera* colony will, if circumstances allow, reproduce in spring or summer by producing a prime swarm and rear new queens in the remaining part of the colony (some of which will leave in after swarms).

We follow this natural development of colonies during the season: our colonies have the opportunity to reproduce (produce drones and swarm cells) when the colonies choose to. However, because we aim to derive four offspring colonies (each with a virgin queen from the mother colony) we avoid losing swarms by making an artificial swarm just before natural swarming would commence. By removing the queen (in an artificial swarm) the production of new queen cells is synchronized. This nevertheless implies that only colonies engaging timely in the reproduction process (by producing a frame with drone brood) will contribute to the next generation. Selection will therefore also be on reproductive abilities (drone and queen production).

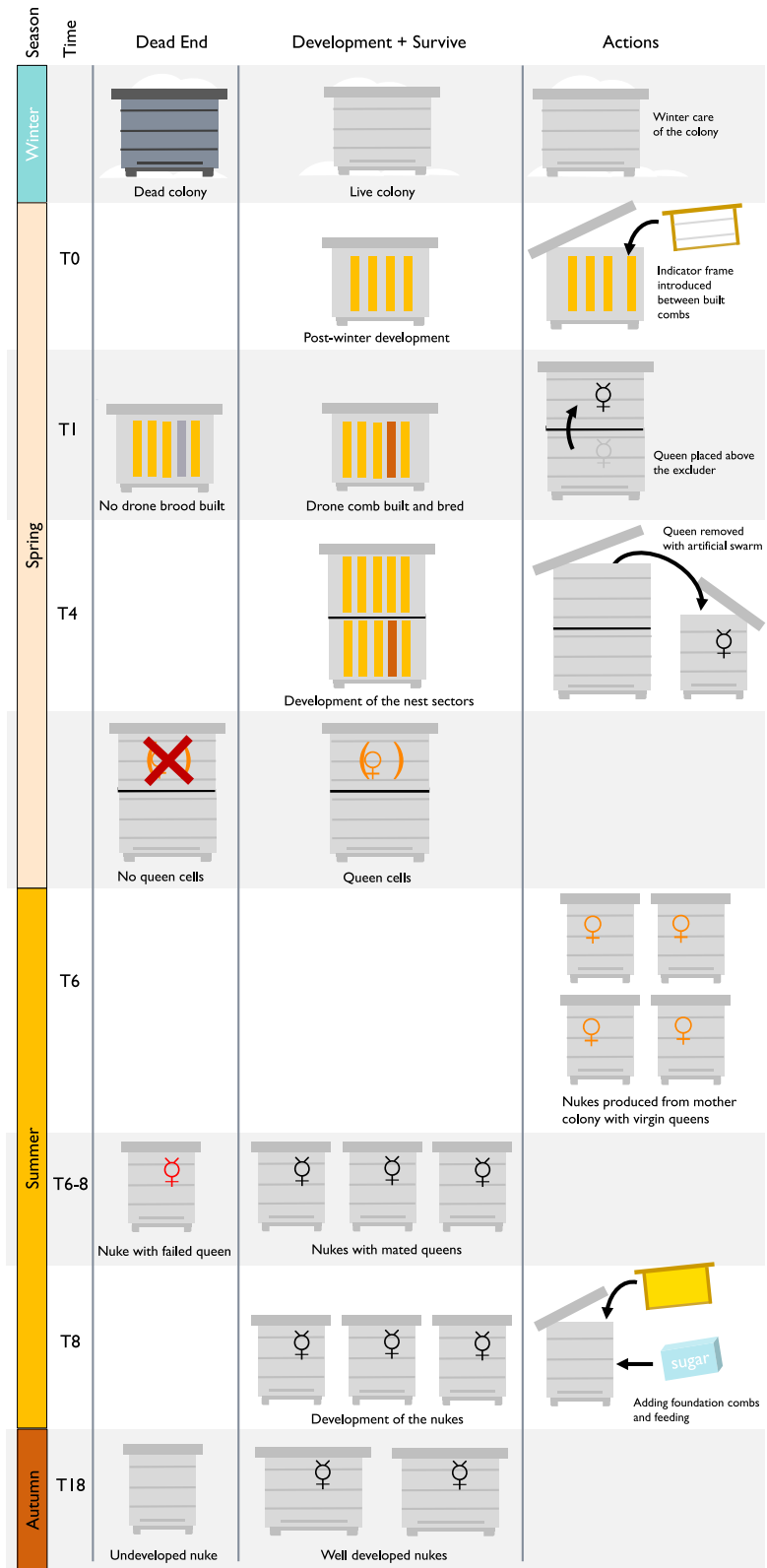
Growth capacity: Selecting for the ability to reproduce (described above) indirectly selects for the ability of the colony to grow in spring, as only colonies that grow and develop well will initiate behaviour associated with swarming. This selection for the capacity to grow is also strong during summer: colonies made in early summer only have 3 months to grow to a sufficient size to survive the subsequent winter.

Survival: The first milestone for survival is the successful mating of the queens. Those colonies that consecutively produce a strong and healthy population of winter bees will have a good chance to survive the winter, and develop further the next spring.

Protocol through the season

Procedural steps taken during the year (Fig. 1), follow the natural development of colonies as much as possible. However they simultaneously ascertain that enough new colonies get raised every season to allow losses through natural selection pressure, and that the most important factor driving selection is the ability of colonies to survive *V. destructor* mite infestations. The steps are not prescriptive, but aim to illustrate the room the protocol leaves to nature to take the selective lead: elimination of non-vital phenotypes after mating, before and during winter and in spring; following natural development as much as possible during the season; only offspring queens from the colony in which they were raised. In the control group of colonies, the possible adaptation of the bees to the *V. destructor* mite is interrupted twice a year (in summer, 2 weeks after making the nucleus colonies,

Fig. 1 Yearly schedule, timing in weeks from T-0 (= time of onset of reproduction cycle, by placing an indicator frame, being a frame with wiring but no wax foundation) and the selective forces survived as well as the selective dead ends (left column) in DBBB



and in winter when no brood is present) by treating the colonies with oxalic acid to kill the phoretic mites. Depending on local conditions and practice, other known efficient treatments may be used (reviewed by Rosenkranz et al. 2010).

Perspective

DBBB is fast, easy, and may uncover traits involved in resistance

Colonies of European *A. mellifera* subspecies are able to survive *V. destructor* infestations by means of natural selection, which has been shown in several instances (Seeley 2007; Le Conte et al. 2007; Fries et al. 2006, reviewed by Locke 2016; Oddie et al. 2017). Since then, several examples of resilience to this mite acquired within an apicultural setting have been published (Panziera et al. 2017; Kruitwagen et al. 2017; Kefuss et al. 2016; Oddie et al. 2017; McMullan 2018). All examples used selection on outcome (survival, vitality (which means well developing colonies), or on (slow) mite population growth), and not on chosen traits such as hygienic behaviour or active grooming behaviour, including the study by Panziera et al. (2017), who used exactly the approach outlined in this article.

Populations of honey bee colonies resulting from these selection approaches apparently have acquired some resistance and/or tolerance to *V. destructor* and can offer a good opportunity to unveil phenotypic traits underlying adaptation to this novel parasite at bee and colony level. Some traits effective at the level of the individual bee may easily be tracked through effects on drones, since drones are haploid. More importantly, such knowledge may help us to understand how parasite resistance in general evolves in honey bees.

Using the proposed approach, we may expect to see significant effects soon (4–10 years), as illustrated by the earlier examples (Panziera et al. 2017; Kefuss et al. 2016; Oddie et al. 2017, 2018; McMullan 2018; Guarna et al. 2017). By allowing selection on drones as well, which is the rule in this approach, selection may proceed even faster, both because drones with susceptible alleles may not be vital and may not mate, and because successful colonies produce a higher number of drones (Jandricic and Otis 2003). An example of fast ‘negative’ selection (elimination of

non-fitting phenotypes, in this case over-aggressive colonies) within a decade has been reported from Africanised honey bees in Puerto Rico, which became as docile as European ones (Avalos et al. 2017).

For hobby/non-professional beekeepers, the approach has a low threshold: it is straightforward and does not need specific equipment. Therefore, it can be done by a single beekeeper or by a local group of (small) hobby beekeepers. According to Jandricic and Otis (2003), it is also cheaper than any targeted selection program. Randy Oliver (2018), a commercial beekeeper in California just started a comparable program including a pre-selection and concluded similarly. The Dutch commercial beekeeping company Inbuzz v.o.f. was able to fulfil such a program together with ten hobby beekeepers for at least 8 years (Van Stratum 2016).

DBBB potential limitations

In order to limit economic losses in the initial years, only a small part of a local population needs to be subjected to this natural selection approach. Beekeepers can continue to manage the majority of their colonies as before. They can, however, raise new queens from the population under selection and thus gradually change the whole population. Since we take advantage of natural selection, there will be no fitness costs for adapted colonies.

Commercial queen breeding as it is applied now does not fit with the suggested approach, because the entire colony is the basis of selection. However, beekeepers using our approach could additionally produce extra queens (in most cases colonies produce > 4 queens), add those to very small mating nukes (e.g. Apidea with a few hundred bees) and let those queens mate at the very same remote location with the rest of the population.

There is a potential for a considerable genetic bottleneck if very few colonies survive from the initial cohort. However, we do not advise total isolation. Therefore, some foreign genes are likely to enter the population. If inbreeding will nevertheless occur, adding colonies might be considered to maintain genetic diversity.

There are fundamental biological differences between Eastern and Western honey bees with respect to *V. destructor* infestations (reviewed by Rosenkranz et al. 2010). For example, successful mite

reproduction in *A. cerana* is restricted to drone brood, which is not a foreseeable scenario for *A. mellifera*. It is therefore apparent that the novel host *A. mellifera* is very unlikely to reach exactly the same level of mite resistance/tolerance as the original one. Nevertheless, the reported levels of naturally selected mite tolerance in populations of European honey bee subspecies (see above) combined with the apparent tolerance of wild and managed Africanized and African honey bee populations to this mite (reviewed by Locke 2016), strongly suggest that the actual level of tolerance which can be reached by *A. mellifera* is apparently sufficient to maintain stable populations.

DBBB works on a local, ‘natural’ scale and will help to avoid the spread of non-native diseases and parasites

Although drones and virgin queens can fly several kilometres for mating, especially at low drone densities (Neumann et al. 1999a, b; Jensen et al. 2005), more than 75% of the matings take place with drones from within the 4.5 km² area around the queen’s hive (Jaffé et al. 2009). With the estimated density of 2.4–3.2 colonies per km² in Germany (Moritz et al. 2007) this would provide queens with 11–15 drone-delivering colonies from within reach. Jaffé et al. (2009) reported median numbers of colonies in reach of virgin queens to be 10–37 in Europe (10–17 in Germany). Thus, starting with 25 colonies and having (due to partial losses) ~ 15 colonies left that do develop well next spring, we have a mating population/colony density very similar to the situation in nature [although numbers are higher in Africa and the Mediterranean (Jaffé et al. 2009)]. The size of the populations should be large enough to avoid inbreeding, and possible bottle-necks will be compensated by balancing selection on the sex locus. This will increase the frequency of rare sex alleles, as was shown in *A. cerana*, after its invasion in Australia (Gloag et al. 2016; Ding et al. 2017). An additional benefit of working in a local area is the possibility of adaptation to the local environment and forage seasonality (Strange et al. 2007), as well as to local disease variants (Blacquièrre and Panziera 2018). A recent transplantation experiment in which colonies of different origins in Europe were compared on reciprocal locations showed how important this may be: local colonies were always performing better than non-local

colonies due to strong genotype–environment interactions (Büchler et al. 2014; Meixner et al. 2014). Is it important to consider that most invasions of bee-parasites and diseases have occurred in conjunction with trade of bees and queen bees (Mutinelli 2011; Owen 2017). Brosi et al. (2017) explained how these immunity-offending practices increase the vulnerability of the bee stock. Because our approach works at a local scale, the chances of importing or exporting diseases and parasites will eventually decrease.

DBBB may increase and conserve the functional genetic diversity of the honey bee population

The western honey bee in large scale apicultural settings was found to have a very high genetic diversity, higher than in ‘original’ endemic populations in Europe (Harpur et al. 2012; Oldroyd 2012), caused by mixing colonies from different original lineages, e.g. M lineage (*A. m. iberica* and *A. m. mellifera*) and C lineage (*A. m. carnica* and *A. m. ligustica*) from Europe (Honey bee Genome Sequencing Consortium 2006). Although this high diversity may look favourable, it might actually be a threat for locally adapted subspecies or populations. Extremely high allelic diversity might slow down balancing selection for polygenic traits. Alternatively, but not mutually exclusive, mating of adapted queens with drones from non-adapted colonies may also increase risks of colony death. Therefore, De La Rúa et al. (2013) strongly call for strict conservation measures to preserve functional genetic diversity through conservation of local subspecies. This conservation will even work at a smaller (more local) scale if our proposed approach will conserve locally adapted populations of bee colonies. This will overall increase the functional genetic diversity of the honey bee, at country- and continent level (which is the sum of local diversities, in contrast to an artificially maintained diversity by a limited number of breeders).

DBBB may help swarms to establish, thereby contributing to re-introduction of honey bees into the wild

A significant proportion of western honey bee, *A. mellifera* populations has always been non-managed (Africa; Jaffé et al. 2009). On feral colonies strong selection pressures act, not only by *V. destructor*.

Being feral may, however, also reduce certain selection pressures in comparison to being managed (Loftus et al. 2016). In cases where the feral population is sufficiently isolated from managed colonies, this can lead to resistance (e.g. Seeley 2007; Le Conte et al. 2007). Often swarms from managed colonies, which become feral, soon die (Thompson et al. 2014), probably because those colonies do not possess genes enabling survival in the absence of mite treatments. However, swarms from the naturally selected population will be more likely to survive because they have acquired resilience to *V. destructor*. Darwin's Black Bee Box might therefore shift the balance between managed and feral colonies by increasing the chances for survival and re-establishment of wild honey bee populations.

DBBB may help the invasion of Varroa destructor to become a successful naturalization

After an invasive species has established, the preferred and chosen path of targeted management, including control/mitigation, may become more costly and troublesome than accepting the inevitable fate that the species has become 'ours' (Epstein 2017). However, being established also implies that the invasive species has become part of 'our' nature, which also opens the challenge for the invasive species to adapt and fit in a new niche as a naturalized species (Blackburn et al. 2011). For the established invasive species *V. destructor*, we propose to gradually abandon targeted management measures and hand the initiative over to natural selection. We therefore call upon beekeepers and scholars to follow our Darwin's Black Bee Box trials, to be started now and in the years to come.

DBBB might work for other invasive parasitic species too

Since evolution by natural selection is universal for all species, it seems evident that this type of approach could in principle be used for other invasive species as well (e.g. for *Tropilaelaps* spp., de Guzman et al. 2017, and for *Nosema ceranae*, Fries 2010). Indeed, in many cases invasive parasite species are controlled by using pesticides, thereby preventing adaptation of the novel hosts (reviewed by Dunn and Hatcher 2015). Given that our scheme can be adapted to these other

cases of invasive parasite species in a meaningful way, taking advantage of natural selection might constitute one sustainable approach for dealing with established parasites and biological invasions in the future.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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