OPINION

Can fungal biopesticides control malaria?

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Abstract | Recent research has raised the prospect of using insect fungal pathogens for the control of vector-borne diseases such as malaria. In the past, microbial control of insect pests in both medical and agricultural sectors has generally had limited success. We propose that it might now be possible to produce a cheap, safe and green tool for the control of malaria, which, in contrast to most chemical insecticides, will not eventually be rendered useless by evolution of resistance. Realizing this potential will require lateral thinking by biologists, technologists and development agencies.

A key component of the integrated control of vector-borne diseases such as malaria and dengue is the use of insecticides that target the insect vectors. However, the utility of insecticides is being undermined by problems of insecticide resistance, environmental contamination and risks to human health[1–3]. Therefore alternative approaches are required[2]. Biocontrol using biopesticides that are based on naturally occurring microbial pathogens is one such method.

Insects can be infected by bacterial, viral, protozoan and fungal pathogens. Of these, fungal entomopathogens are perhaps the most well suited for development as biopesticides because they do not require ingestion by the host. Instead, these fungi infect by external contact with the host (FIG. 1). The time taken to kill the host following infection varies from 2 to 5 days to a few weeks, depending on the particular host–pathogen combination and environmental conditions[4].

Few biopesticide products have been widely used, despite their potential. Indeed, on a global scale, penetration of biocontrol technology into the pesticide market has been minimal; biocontrol constitutes less than 2% of global pest-control sales (US$30 billion annually), and >70% of this small proportion are biopesticide products that are based on the crystal-toxin-forming bacterium *Bacillus thuringiensis*[5,6].

This failure to adopt biocontrol strategies raises a fundamental question: is the success of microbial biocontrol limited by inadequate technology, unfavourable economics or a complex interplay of several factors? In this article we draw on recent advances in the development of biopesticides based on entomopathogenic fungi to explore this question. We use insights from the recent successful development of biopesticides for the control of locusts and grasshoppers to examine the potential for development of a biopesticide to infect mosquitoes in resting and breeding sites in residential settings.

Biopesticides for locusts and grasshoppers

In 1989, in response to concerns over the environmental and human-health consequences of extensive chemical applications against locusts and grasshoppers in Africa, the international donor community supported the initiation of a collaborative research programme to develop a more sustainable, biological pesticide for locust and grasshopper control. The programme, named LUBILOSA (Lutte Biologique Contre les Locustes et les Sauteriaux), was founded on preliminary research that had identified a virulent strain of the entomopathogenic fungus *Metarhizium anisopliae* var. *acridum*, and had revealed how formulation of fungal spores in oil could enable infection in conditions of very low relative humidity[7–9] (FIG. 2). The product developed was Green Muscle (a registered trademark), which has now been registered in several countries including South Africa, Zambia, Namibia, Sudan, Mozambique and much of French West Africa. Since LUBILOSA ended in 2001, several projects have continued to evaluate the impact of Green Muscle on locust and grasshopper species in Africa and Europe, to optimize its usage[9].

In 1993, the Commonwealth Scientific and Industrial Research Organisation (CSIRO) collaborated with LUBILOSA to develop a biopesticide (based on an Australian strain of the same subspecies used in Africa) for use against locusts and grasshoppers in Australia[10,11]. This resulted in Green Guard (a registered trademark), which was registered in Australia in 2005 (REF. 11). Green Guard now forms an integral part of locust-control operations in Australia, with a steadily increasing market share as the technology has become established[11,12].

The production of Green Muscle and Green Guard show that effective biopesticide products based on entomopathogenic fungi can be developed. The LUBILOSA programme cost ~US$17 million, which compares well with the estimated US$70–100 million that is required to develop a new synthetic pesticide compound[9]. Although there are some cheaper products available, Green Muscle and Green Guard are competitively priced compared with most established insecticides. Importantly, out of all the products used for locust and grasshopper control, they have the lowest environmental impact and can be used near water courses, organic crops and conservation areas, satisfying the demand for more environmentally sustainable technologies.

More generally, the locust biopesticide programmes have advanced our knowledge in a range of areas such as isolate screening, formulation, mass production, quality control, storage, application, environmental impact, safety testing and host–pathogen ecology. These technical advances have been accompanied by developments in capacity in

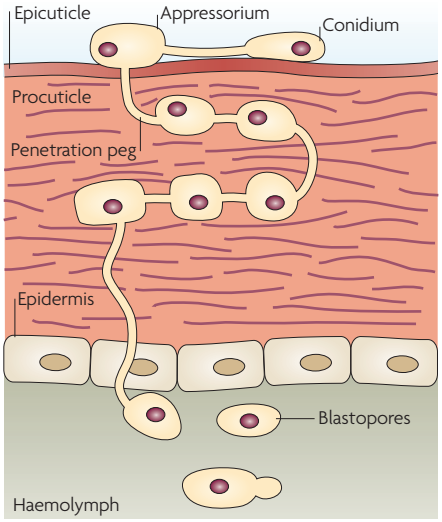

Figure 1 | **Infection by fungal entomopathogens.** The *in vivo* development cycle of entomopathogenic fungi, such as *Beauveria bassiana* and *Metarhizium anisopliae*, involves sequential steps. First, conidia (spores) adhere to the host cuticle, then the conidia germinate and the germ tube and appressorium (penetration structure) are produced. The cuticle is penetrated by a combination of mechanical pressure and the action of cuticle-degrading enzymes. The fungus grows by vegetative growth in the host haemocoel and external conidia are produced upon the death of the host[65,66]. The host cuticle is the first line of defence against infection and has a central role in determining fungal specificity. If the fungus breaches the cuticle, successful infection can only result if the fungus can overcome the innate immune response of the insect. Insects respond in both a cellular and humoral manner to fungal infection, with immune activation occurring as early as the point of cuticle degradation during the penetration step[65]. Fungi have two main strategies for overcoming host defence responses; development of cryptic growth forms that are effectively masked from the insect defence responses, and production of immunomodulating substances that suppress the host defence system[65,66].

areas such as commercial production and distribution, product registration, and extension to end-users. Overall, such initiatives provide a solid foundation for the development of fungus-based biopesticides for use in integrated strategies for the control of diseases such as malaria, dengue and filariasis.

Proof of concept for malaria control

Several studies have investigated the use of microbial biocontrol to kill mosquitoes (for reviews, see REFS 13–15). Typically, virulent pathogens have been isolated, with the aim of developing biopesticides to kill mosquito larvae[13,14,16]. More recently several studies have highlighted the potential use of fungal pathogens to kill adult mosquitoes[17–20]. The common approach behind these studies is to infect insects by exposure to oil-formulated fungal spores that have been applied to surfaces on which adult mosquitoes rest after blood meals.

Initial laboratory-based bioassays revealed that mosquitoes were readily infected by exposure to entomopathogenic fungi and that some fungal isolates caused 100% mortality of adult *Anopheles* and *Culex* spp. in 7–14 days, depending on dose, formulation and fungal strain[17–19]. Further studies used a rodent model of malaria to examine the effect of fungal infection on malaria transmission potential[19] (FIG. 3). The results indicated an 80-fold reduction in the number of mosquitoes able to transmit malaria following exposure of the insects to the fungal pathogen. This reduction resulted from two complementary effects of fungal infection.

First, fungal infection caused high levels of mosquito mortality by day 14 after blood feeding (when sporozoites are present in the mosquito mouthparts). Moreover, the daily mortality rate of mosquitoes infected with both fungus and malaria increased compared with insects infected with just the fungus from day 11.

Second, significantly fewer surviving mosquitoes had sporozoites in their mouthparts compared with control mosquitoes infected with malaria alone, which indicates a negative effect of fungal infection on survivorship/development of the malaria parasite inside the mosquito. In addition, fungus-infected mosquitoes were less likely to blood-feed (FIG. 3), further reducing transmission potential[19,21].

Finally, a small-scale study in village houses in Tanzania confirmed the feasibility of infecting mosquitoes with virulent fungi under field conditions in Africa[20]. This investigation used a relatively low dose of an experimental formulation applied over a small surface area, but still showed that 34% of mosquitoes collected from targeted village houses were infected with fungi. Simple epidemiological models predict that even this relatively low level of infection would result in a 75% reduction in entomological inoculation rate at this field site[20]. The study used fungus-treated black cloths that were pinned to the ceilings of dwellings. These cloths were repeatedly treated with spores at relatively little cost or inconvenience.

These studies highlight the potential of fungal biopesticides to substantially reduce mosquito vectorial capacity using currently available technology. However, the literature is littered with examples of promising microbial agents and candidate biopesticide technologies, but, as evidenced by the limited penetration of the chemical-pesticide market, little of this potential is realized.

Figure 2 | **Biopesticides for the control of locusts and grasshoppers in Africa.** A virulent strain of the fungal entomopathogen *Metarhizium anisopliae* var *acridum* was isolated from an infected cadaver collected from the field (panel **a**). Spores are located on the inter-segmental membranes. Simple techniques have been developed for *in vitro* mass production. Panel **b** shows a small-scale production facility in West Africa in which spores are grown in bowls using part-cooked rice as a solid substrate. Fungal spores are then harvested from the rice (panel **c**) and formulated in oil for ultra-low-volume application using hand-held (panel **d**), vehicle (panel **e**) or aerial-mounted (not shown) sprayers. Infected locusts and grasshoppers typically die in 7–25 days (panel **f**) — the speed of kill is strongly influenced by environmental temperature and insect thermal behaviour in this system[4] — and under conditions of high humidity infected insects produce new spores. Images were kindly supplied by the LUBILOSA programme.

So, here we consider some of the features that represent both the strengths and weaknesses of the fungal-biopesticide approach. We draw on lessons learned from the locust-biopesticide research and consider specific aspects relating to biopesticide control of malaria. As such, we do not consider more generic, albeit important, research and development issues such as optimization of production, delivery systems, field testing or safety issues (for a discussion of these see REFS 22–24).

Disease pathology and biopesticides

A crucial factor for the successful transmission of malaria is the longevity of the mosquito compared with the approximately 2-week parasite incubation period[25,26]. Even small reductions in adult mosquito longevity after an infective blood meal can have a large effect on the dynamics of the malaria parasite. So, unlike most other insect-control problems it is not necessary to rapidly kill the mosquito with a virulent pathogen. Moreover, emphasis on the 'pesticidal' properties of entomopathogens overlooks their potential to influence insect behaviour and fitness in subtle ways that could also negatively affect malaria transmission without necessarily reducing vector density. For example, numerous insect–pathogen studies have highlighted the potential for sub- or pre-lethal pathogen effects. Locusts that are infected with entomopathogenic fungi develop alterations in several characteristics before death, such as feeding behaviour, fat-body accumulation, development rate, fecundity, mobility and predator-escape responses[27–31].

Similarly, as described above, preliminary research indicates that infected mosquitoes might have a reduced propensity to feed prior to death[19,21], and there is evidence that fungal pathogens can affect not only the mosquito, but also the survivorship of the malaria parasite within the mosquito[19]. The mechanisms that underlie this anti-malaria effect are unknown but might include alterations in host nutritional balance, which lead to resource competition, upregulation of immune responses, or production of secondary metabolites in the haemolymph.

The deleterious effects of sub-lethal pathogens on the capacity of insects to function as vectors of disease have been virtually ignored, although sub-lethal effects are the most common outcome of infection. Exploiting the sub-lethal effects of pathogens could present new opportunities for the development of biopesticides.

Evolution of resistance

Anopheles spp. mosquitoes have proved adept at evolving resistance to chemical insecticides[32–34]. Indeed, resistance to insecticides has appeared in the main insect vectors from every genus, with examples of resistance to every chemical class of insecticide[35]. Biopesticide control would be similarly unsustainable if the widespread use of fungal entomopathogens provided a selective pressure that resulted in the evolution of fungal-resistance mechanisms in mosquitoes[22,36].

Little is known about genetic variation in fungal susceptibility among *Anopheles* spp. populations. All mosquitoes might be fully susceptible (we can find no records of complete resistance against fungal pathogens

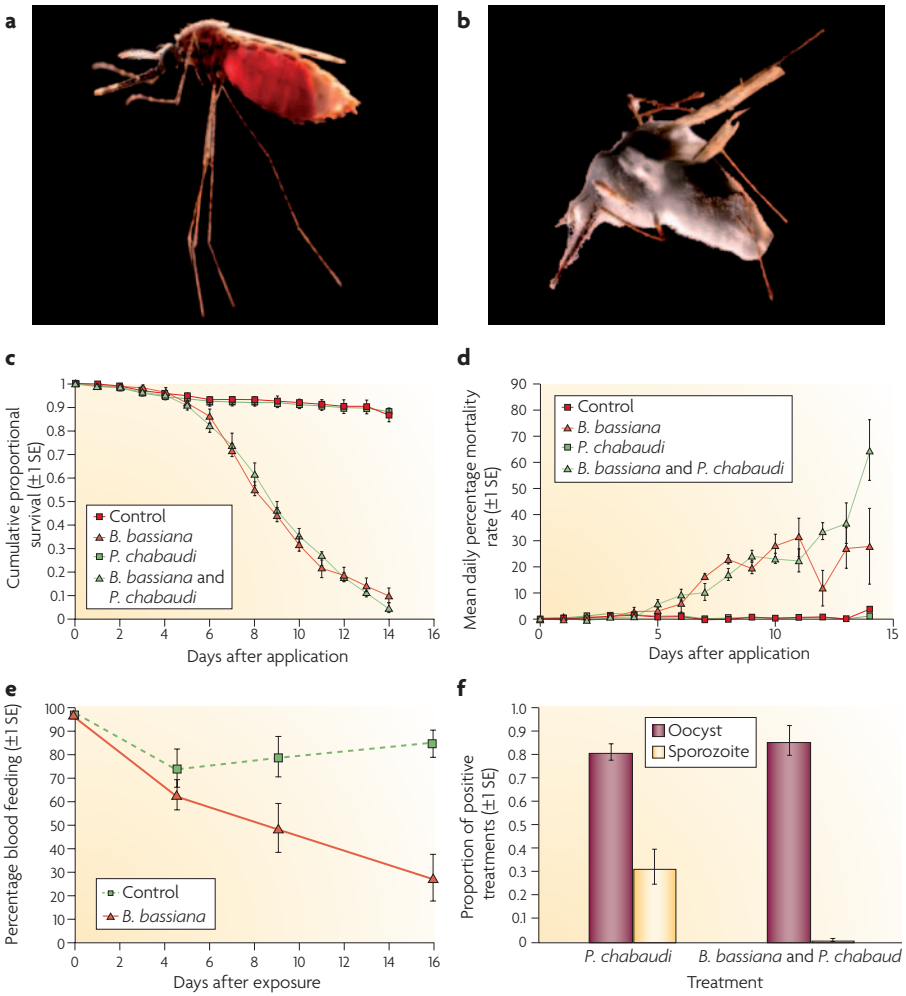

Figure 3 | **Fungal infection reduces malaria transmission by mosquitoes. a** | Female mosquitoes contact fungal spores from treated surfaces as they rest to digest a blood meal. **b** | As the fungal infection progresses, mosquitoes die. In the correct conditions, a mat of fungal spores is deposited on the outside of the cadaver. **c** | Infection with the entomopathogenic fungus *Beauveria bassiana* dramatically reduces survival of *Anopheles stephensi* mosquitoes by day 14 (the time following an infectious blood feed at which an individual mosquito becomes able to transmit malaria). **d** | In addition, there is an interaction with malaria parasites (*Plasmodium chabaudi*) whereby daily mortality rates accelerate from day 11 in those mosquitoes carrying both fungus and malaria. **e** | Mosquitoes infected with the fungus show a significant decline in their propensity to blood feed as the disease progresses[19]. **f** | Survivorship or development of the malaria parasite inside the mosquito is affected such that, even if mosquitoes survive, there is less chance that they will contain infectious sporozoites in their mouthparts. The figure shows the mean (± SE) proportion of the starting population of mosquitoes in the *P. chabaudi* and *P. chabaudi* and *B. bassiana* treatments that are positive for *P. chabaudi* oocysts at day 7 and sporozoites at day 14 after an infectious blood meal. The effect is an 80-fold reduction in the potential of mosquitoes to transmit malaria. Panels **c**, **d** and **f** are reproduced with permission from REF. 19 © (2005) American Association for the Advancement of Science. Panels **a** and **b** were kindly supplied by Hugh Sturrock, University of Edinburgh, UK.

in any insect). However, there is evidence for genetic variation in susceptibility (time to death) to entomopathogenic fungi in aphids[37,38] and *Drosophila melanogaster*[39], as well as environmentally and behaviourally mediated host responses that alter effective resistance[4,40–42]. Moreover, in the long history of attempts at malaria control, resistance to all interventions has eventually evolved, even in the absence of pre-existing resistance. If biopesticides are to avoid the depressing fate of so many other malaria-control measures, we need to maximize the reduction in malaria transmission without imposing strong selection on vector populations. There are several reasons for thinking that this might be achievable with a fungal biopesticide.

First, the negative effects of pathogenic fungi on the mosquito host occur relatively late in the life cycle of the mosquito. Fungal-induced mosquito mortality and reduced propensity to blood feed occur after most mosquitoes in natural populations have already died (FIG. 4). It is well known in the context of the evolution of ageing that beneficial mutations acting late in life are subject to weak selection because they confer fitness benefits after most individuals have ceased reproducing[43,44]. So, even if *Anopheles* spp. could develop resistance to fungi, biopesticides might impose only weak selection for that resistance. Such a reduction in selection pressure could translate into additional decades of effective product use. Moreover, there might actually be no selection for resistance. If the possession of fungal-resistance mechanisms entails metabolic costs, all individuals in a population would pay the price for a benefit that is experienced only by a few. Indeed, although it might be tempting to deploy more virulent isolates that either kill insects more quickly, or kill insects at a constant daily rate, the capacity for killing would need to be balanced against potentially sharp increases in selection pressure to evolve resistance.

This argument is subject to a couple of corollaries. Slow speed of kill potentially increases the level of biopesticide coverage that is necessary to affect malaria transmission, because the slower the speed of kill,

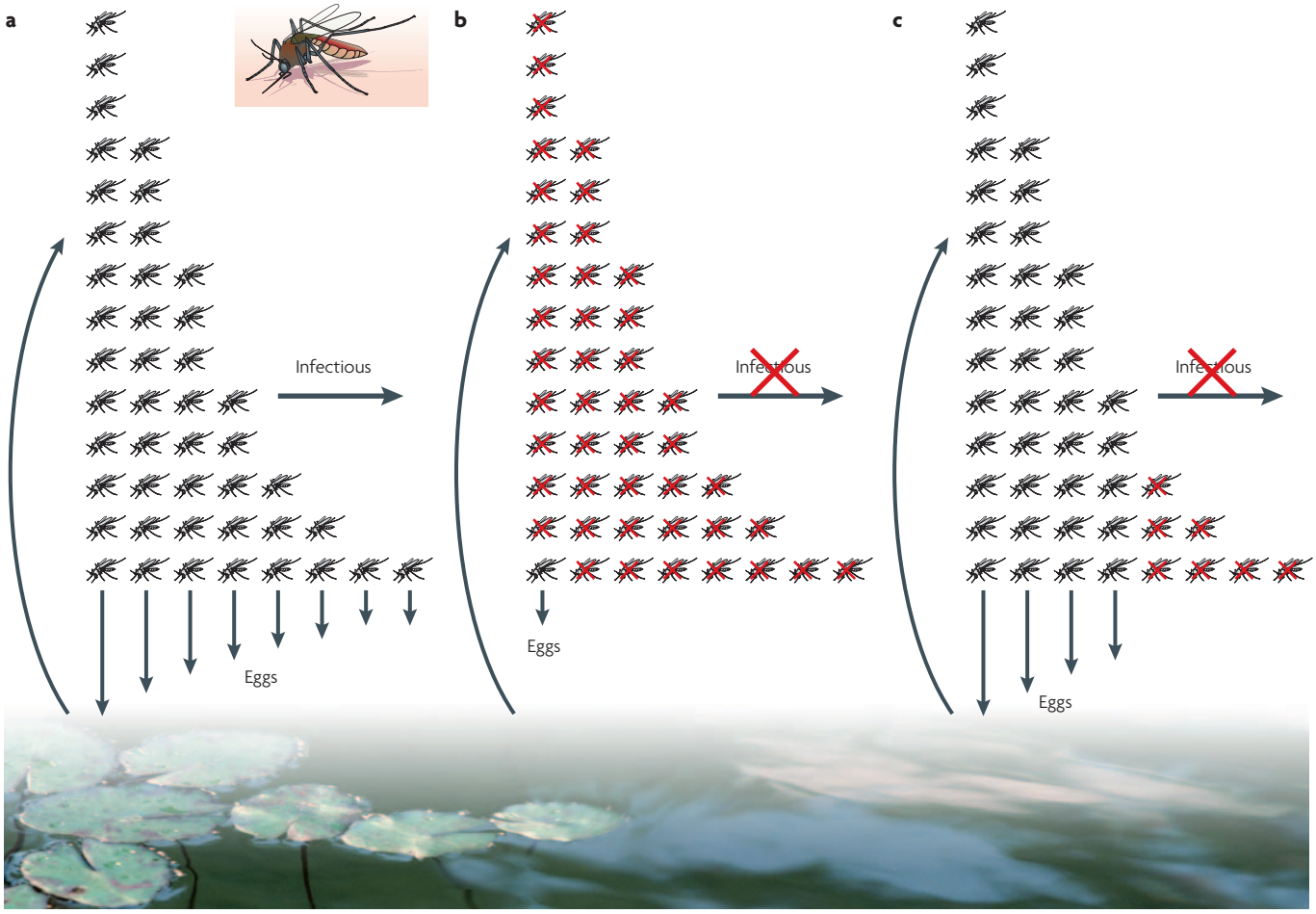

Figure 4 | **The sustainability of chemical and biological interventions against adult mosquitoes. a** | Female mosquitoes usually take a blood meal every 2–4 days and use this to mature an egg batch. Natural mortality is generally high, therefore most of the reproductive output (vertical arrows) from a population accrues over the first 1–3 feeding/oogenic cycles. Relatively few mosquitoes actually survive long enough (12–14 days) in the field for the malaria parasite to complete its development, migrate to the mosquito mouthparts and get transmitted to a new human host ('infectious'). **b** | Exposure to a fast-acting insecticide following the first blood meal reduces survivorship and prevents malaria transmission. However, the rapid mortality carries a big fitness cost and creates a substantial selection pressure for developing resistance. **c** | A relatively slow speed of fungal kill helps mitigate selection pressure because infected mosquitoes can still complete the early oogenic cycles. An isolate that allows a high level of survival (and hence egg production) over the first 7–9 days, for instance, but then causes extensive mortality will still reduce malaria transmission but will impose little selection for resistance.

Box 1 | **Paratransgenic approaches**

Although there is a wealth of lethal and sub-lethal properties of natural fungal isolates (or isolate combinations) to be explored, there is also considerable additional promise for using residual sprays of fungal pathogens in novel paratransgenic approaches. Regulatory and ethical concerns notwithstanding, as fungal pathogens function by contact with the insect host they could constitute a novel delivery mechanism for anti-malarial or anti-mosquito biomolecules. Genetic modification could enable fungal pathogens to express toxins or, for example, effector molecules that block sporogony within the insect vector[60]. Lack of a practical delivery mechanism has been identified as a significant constraint for malaria-control interventions that might exploit mechanisms such as RNA interference[61]. However, the potential to transform fungal entomopathogens is well established. For example, *Metarhizium anisopliae* has been engineered to over-express a toxic protease that increases the speed with which it kills lepidopteran pests in agricultural systems[62]. Secondary transfer of fungi from mosquitoes is unlikely to occur — fungal spores are only produced once the insect is dead, and many cadavers are scavenged before sporulating — so fungal transgenes would be easier to control than mosquito transgenes. Moreover, whereas the spread of transgenes in mosquito populations is fraught with ecological and population-genetics problems[63,64], the fitness of the transgenes (the ability of a modified gene to persist and spread throughout a population) would be relatively unimportant in a biopesticide in which repeated application is envisaged and natural reproduction and transmission are of little consequence.

the greater the need for the mosquito to become infected at the first or second blood feed. This will require that a high proportion of houses are treated and that there is a high probability of infection per feed. Fungal pathogens might also place an evolutionary pressure on the malaria parasite to produce sporozoites before the fungus kills the host[36]. However, given that natural mosquito survival is so low, there must already be strong selection for more rapid development. There must, therefore, be substantial fitness costs associated with shorter incubation periods. Even if fungal biopesticides did tip the balance in favour of more rapid development, it is difficult to assess the overall effect on human disease burdens of any such evolution without knowing what these fitness costs are.

A second reason for thinking that fungal biopesticides would not be undermined by mosquito resistance is the possibility that fungal infection has a direct anti-malarial effect, which reduces the prevalence of sporozoites. It would be highly desirable to isolate fungal strains that had an increased propensity to reduce mosquito infectiousness, as this effect of the pathogen does not result in selection for fungal resistance in mosquitoes. Indeed, some fungal isolates can reduce sporozoite prevalence without causing any mosquito mortality (S. Blanford, A.F.R and M.B.T., unpublished observations); this effect could, in principle, be enhanced by paratransgenesis (BOX 1). However, products relying only on these anti-malarial effects might in the long run suffer from the evolution of resistant malaria parasites.

A third reason for thinking that biopesticides could be evolution-proof, is that mosquitoes infected with malaria parasites are more likely to die following fungal infection than mosquitoes that are not infected with the parasite (FIG. 3). Malaria-infected mosquitoes normally constitute less than 10% of the insect population. If the main effect of a fungal isolate was to reduce the fitness of malaria-infected mosquitoes (rather than all mosquitoes), this should reduce selection pressure for fungal resistance across the entire mosquito population, and might even select for increased malaria refractoriness[45]. Again, this would reduce malaria transmission without imposing a selection for fungal resistance.

Even if fungal resistance is unlikely to emerge in response to biopesticide use, it would still be extremely interesting to understand mechanisms of fungal resistance in mosquitoes. For instance, are any resistance mechanisms specific to particular fungal isolates or strains? If there are such specific resistance mechanisms, combinations of fungal strains could be used in single biopesticide formulations to minimize further the risk of evolution of resistance. In any case, owing to the nature of fungal infection and the resultant insect immune response, it seems extremely unlikely that resistance to fungi resistance would be related to 'metabolic' or 'knock-down' insecticide resistance mechanisms, so it should be possible to use biopesticides in localities in which evolution has rendered chemical insecticides obsolete.

Formulation and application

The application of spores inside houses, where many malaria-vector species prefer to

Glossary

Appressorium
A flattened, hyphal 'pressing' organ that is produced by a germinating fungal spore, from which an infection peg grows and penetrates the host cuticle.

Biocontrol
(Also 'biological control'.) The use of live natural enemies such as predators, parasitoids or pathogens to control pest insects, weeds or diseases. The normal ambition is that the introduced organism will be self-sustaining, but it can also include inundative approaches which need not be self-sustaining, as with biopesticides (see below).

Biopesticide
In simplest terms, refers to a pesticide that is biological in origin (that is, viruses, bacteria, fungi). The approach is characterized by repeated applications of a live organism with little or no reliance on the organism to reproduce or be self-sustaining in order to effect control. The biocontrol agent is essentially used as a chemical-pesticide analogue.

Entomological inoculation rate
(EIR). A measure of the frequency with which a human is bitten by an infectious mosquito.

Haemocoel
The body cavity of an arthropod in which most of the major organs are found. It is filled with the arthropod equivalent of blood, named haemolymph.

Oocyst
A walled, vegetatively replicating malaria parasite under the basal lamina of the mosquito midgut in which the transmissible sporozoites form.

Parasite incubation period
The time from infection of the mosquito — following a blood feed from a human host carrying malaria — to the point at which the mosquito is infectious and can transmit the parasite to a new host during a further feeding bout. Throughout large areas of malaria transmission the parasite incubation period is 12–14 days or longer.

Paratransgenic approaches
(Or paratransgenesis.) Genetic manipulation of vector-associated organisms — commensal or symbiotic bacteria, or fungal entomopathogens — to alter the ability of the vector to transmit a pathogen. The insect vector itself is not genetically modified.

Sporozoite
Small elongated cells that arise from repeated division within the oocyst. The malaria sporozoites accumulate in the salivary glands and are introduced into the blood of the vertebrate host by the mosquito bite.

Vectorial capacity
Provides a measure of disease risk as determined by the ability of a vector to successfully transmit disease, and incorporates vector competence, abundance, biting rates, survival rates and parasite incubation period.

blood-feed and rest, optimizes the likelihood of fungus contact and infection. Persistence of the fungal pathogens on treated surfaces is a key factor that will determine the ultimate success of the biopesticide approach[46].

The active ingredient of a biopesticide is a living organism, so there will be biological limits to its persistence. We must not expect that a biopesticide can, or necessarily should, have persistence characteristics similar to, for example, the long-lasting insecticide-treated nets, which can remain effective for several years[47].

Preliminary studies indicate that viable spores can be recovered from treated surfaces after 3 months, but that the percentage infection of mosquitoes exposed to these 3-month-old surfaces is low (S. Blanford, A.F.R. and M.B.T., unpublished observations). However, studies on the use of fungal pathogens to control tsetse fly (*Glossina fuscipes*) in Kenya indicate that spores retain their viability for 31 days in the field without affecting efficacy against *G. fuscipes*[48]. Moreover, studies on spore storage indicate that fungal spores can remain viable for more than 12 months, depending on the prevailing temperature and humidity [49,50]. So, there is scope for achieving long-term infectivity, but there is little understanding of the variation in infective half-life between different fungal strains. Nor do we fully understand to what extent fungal persistence is determined by biological variation, versus factors such as dose and formulation under different environmental conditions. A fungal isolate that is only moderately pathogenic, but that persists and remains infectious, could ultimately be more useful as a biopesticide than an isolate that is highly virulent, but requires reapplication every 2 weeks. Similarly, an isolate that is easy to mass produce could prove more effective (both in terms of economics and impact) than an isolate that is more virulent but difficult to produce in operational quantities. The amenability of candidate microbial agents for commercial development has been identified as a critical factor in determining biopesticide success, but is rarely considered as a criterion in isolate selection[51].

One area where there is substantial scope for maximizing infectivity and persistence is through formulation. There is generally little specialist research on the formulation of microbial agents[52]. However, the agrochemical, pharmaceutical and food-processing industries have considerable expertise in producing formulations that enhance shelf-life, protect products from decay and UV radiation, and enable targeted or slow release of an active ingredient. The novel application of these established technologies could revolutionize biopesticide use[52].

Technology transfer and implementation

In Australia, Green Guard was used to treat >60,000 Ha of locust infestations during the 2005–2006 season[12]. Adoption of Green Muscle in Africa, on the other hand, has been much more patchy. There are several factors contributing to the contrasting situations on the two continents, including differences in socio-economics, capacity, socio-political complexities and government and donor commitment[9,53]. The important insight, however, is that successful implementation and adoption require more than just technological innovation.

Studies on the demand for malaria-control interventions indicate correlations between willingness to pay and socio-economic status[54] and potentially low threshold costs for deriving net benefit from control technologies[55]. On the basis of the current costs of products such as Green Muscle and Green Guard, and the experimental dose rates used in the initial evaluation of fungi for the control of malaria[19], we estimate that it would cost approximately US$0.01 for enough biopesticide product to treat 1 m^2. This is an encouraging figure, although it does not include labour costs, the cost of cloth or netting for impregnation, and so on, so total cost will still be a significant factor, including the question of who pays for the biopesticide. Both locust-control biopesticides ultimately followed a public–private partnership model, which engaged small-to-medium-scale commercial companies to produce and distribute the products at national or regional levels. However, although they require good quality control[56,57], the methodologies for mass production are inherently 'low-tech' (FIG. 2). Local- (or even village-) scale production of biopesticides might be feasible, which would contribute towards ownership and acceptance of the technology at the community level. Such 'bottom-up' approaches are impossible with chemical insecticides, but evidence indicates that control programmes are most successful when there is good local cooperation owing to education, training and community involvement in implementation[58]. This need for cooperation identifies an important role for participatory approaches, with end-users engaged early in the development process; something which is now recognized in the WHO policy for integrated vector management[59].

Moreover, it is also important to match use (and user expectation) with product specification. Areas differ substantially in the seasonal incidence of malaria and their epidemic-versus-endemic status. In some settings, two or three treatments of even a short-persistence product could provide affordable, year-round control. Other settings might require repeated monthly applications which could prove prohibitive, depending on capacity and socio-economic context. An alternative strategic approach would be to use a biopesticide over restricted temporal or spatial scales to disrupt cycles of resistance evolution and increase the durability of existing chemical interventions. This would represent a highly innovative application of biocontrol and could dramatically alter the cost:benefit ratio of the technology.

Concluding remarks

The successful development of biopesticide products for locust control demonstrates the potential for the translation of research into practice. Although this took several years, technical and regulatory developments should enable new applications, such as mosquito control, to reach the market more rapidly. The specific features of fungal infection such as late-acting mortality, transmission blocking and host behavioural changes, provide opportunities to minimize the risk of resistance evolution. Indeed with fungal biopesticides, we are perhaps in a unique position in the history of malaria control: we can think about preventing evolutionary outcomes now, rather than after a once-promising method has begun to fail. There is also scope for innovative applications of knowledge from other industries. Nonetheless, numerous research challenges remain and we need to recognize that there will be technical and biological constraints that set limits to the approach. Moreover, contrasting experiences with the locust biopesticides in Africa and Australia reveal the need to support not only research and development but also, implementation and capacity building. To make such technologies an effective reality we cannot simply rely on the initial technical innovation and market pull. This is an important interdisciplinary interpretation that sets a challenge to both the researchers working to develop alternative pest-control technologies and the donors and agencies that support their activities.

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Competing interests statement
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