


Gene drives, species complexes, and the risks of collateral damage

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The development of engineered gene drive systems continues to garner significant interest. Theoretically, these systems could spread traits in a target species (an approach known as population replacement) or eliminate a population within a few generations (population suppression). Some researchers have promoted this disruptive technology for potential applications ranging from public health (e.g., malaria control) to conservation (e.g., protection of endangered species, elimination of invasive ones) to agriculture (e.g., pest control).

But in the case of a gene drive intended to target a specific species, the risk of affecting non-target species must be taken into account, and researchers must strive to minimize collateral damage. Hybridization between a target and a non-target species could result in unintended gene flow, as could the horizontal transfer of the gene drive cassette (1).

While some researchers have proposed the “Target Species Complex” (TSC) framework to account for off-target effects, the concept is unlikely to provide a safeguard. Rather, it risks reframing collateral impacts as intentional outcomes, narrowing, rather than broadening, the scope of ecological and regulatory considerations. Researchers must therefore make sure to incorporate risk assessments that take into account the effects on numerous species and make a concerted effort to understand the downstream effects.

A gene drive introduced into the malaria-transmitting *Anopheles gambiae* mosquito could, in principle, spread to mosquito species that are not of epidemiological importance. It's essential that gene drive projects account for all potential risks. Image credit: Science Source/CDC/James Gathany.

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Author contributions: C.B. designed research; performed research; and wrote the paper.

The author declares no competing interest.

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Any opinions, findings, conclusions, or recommendations expressed in this work are those of the authors and have not been endorsed by the National Academy of Sciences.

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Published November 5, 2025.

Advances and Risks

Gene drive technology is most advanced in *Anopheles* mosquitoes (2), with work being mainly conducted on *Anopheles gambiae* s.s., *Anopheles coluzzii*, and *Anopheles arabiensis*. Interestingly, the *An. gambiae* complex consists of at least nine closely related mosquito species, some of the them having been described as a species only recently, such as *An. fontenillei* sp. (3). Among these, some are major vectors of malaria (*An. gambiae* s.s., *An. coluzzii*, *An. arabiensis*), while others (*An. quadriannulatus*, *An. bwambae*, *An. fontenillei*) are believed to play little or no role in malaria transmission. Hybridization occurs between several of these species, with fertile hybrids occurring not only in the laboratory (4), but also in the field (5), including between *An. gambiae* s.s., *An. coluzzii*, and *An. arabiensis* (6). Hence, a gene drive introduced into *An. gambiae* s.s. could spread to these other species, even though they are not of epidemiological importance.

A similar approach targeting not just a single species, but potentially an entire species complex has been extended beyond gene drives. For example, developers of precision-guided sterile insect technique explicitly describe the approach as “species-specific or species complex-specific,” acknowledging its potential to suppress not only *An. gambiae*, but also sibling species within the complex (7). The notion that genetic control tools may inherently operate at the level of species complexes further blurs the line between intended and collateral modification. And this raises important considerations, as gene flow between species could lead to the unintended spread of genetic constructs beyond the target population.

The assumption that modifying an entire species complex will yield only beneficial outcomes is scientifically misleading, overly reductive, and ecologically risky.

At first blush, gene drive researchers seem to have addressed this concern. Aware of hybridization inside the *An. gambiae* complex, developers of gene drives targeting the highly conserved doublesex locus in *Anopheles* mosquitoes as part of their suppression approach (8) have introduced a novel concept: the TSC. In this framework, the target is not only a given species anymore, but the whole complex within which it is embedded. The TSC acknowledges that gene drive constructs may not be strictly confined to a single species but spread beyond it due to hybridization and genetic compatibility within a group of closely related species.

However, the TSC is not enough. The scope of risk assessment—i.e., the range of species—must be broadened. Rather than focusing only on one target species and implicitly excluding others, risk assessments should include all species within the complex, even the ones that have not been described yet, since they could also experience gene drive effects. A non-target species of interest (2) would represent a stepping stone toward a broader genetic delivery throughout the whole complex, potentially serving as a convenient delivery system.

The TSC notion could potentially be interpreted as a deliberate modification of nonvector sibling species for the purpose of modifying one or several vector species. In other

words, collateral damages would be openly accepted. The intervention, as a result, becomes an intentional, large-scale genetic modification of entire species complexes. The collapse of this barrier between target and non-target species preemptively reclassifies unintended consequences as strategic gains. This not only downplays potential ecological disruptions, but may also reduce regulatory scrutiny, setting a troubling precedent for large-scale genetic interventions.

Ethical and Ecological Blind Spots

The assumption that modifying an entire species complex will yield only beneficial outcomes is scientifically misleading, overly reductive, and ecologically risky. It ignores a central point in ecology: ecosystems are networks of interdependent relationships, not isolated units. Modifying the genetics of one species or a group of closely related species can indeed lead to unpredictable cascading effects destabilizing ecosystems.

One obvious concern is the disruption of ecological roles. Although species complexes consist of a collection of morphologically similar organisms, they are ecologically diverse. Indeed, within a complex, species could play different and critical roles in ecosystems as pollinators, predators, prey, or competitors. Suppressing or genetically altering a species without differentiating between these roles risks undermining ecological functions.

For example, the removal of a species involved in pollination might inadvertently affect plant reproduction and, as a result, the species that depend on those plants. Complicating matters, ecological assessments also often fail to account for unknown biodiversity, simply because it has not been described yet. The lack of information about a given species increases the risk that gene drive developers could unknowingly spur ripple effects throughout the ecosystem.

Hybridization and Evolutionary Uncertainty

Species hybridization, the mechanism that allows a gene drive to spread across a species complex, is also a source of evolutionary uncertainty. Hybridization allows for genetic material to move beyond a single target species; it also opens the door to unintended evolutionary dynamics. Selection pressures could drive the evolution of resistance or lead to unexpected genetic interactions. Moreover, increasing the effective size of the target population may raise the likelihood of compensatory mutations, thus making the target species not only more resilient to suppression, but also harder to control. Rather than controlling a species, the intervention might enhance its resilience, undermining both ecological safety and practical efficacy.

Hybrid species created as a result of gene drive could have unpredictable ecological traits that make them more invasive, harder to control, or lead to negative epidemiological consequences. This is not just theoretical, but highlighted by the hybridization between *Culex pipiens* and *Culex quinquefasciatus* mosquitoes on Madera. This hybridization may have promoted a more opportunistic feeding behavior, thus contributing to the human transmission of zoonotic arboviruses such as West Nile Virus (9).

Horizontal gene transfer (HGT) adds a further wrinkle. In recent years, researchers have shown that HGT occurs in insects (10) and even between plants and insects (11). Growing evidence highlights its role as a significant driver of genetic novelty. In genetic systems designed to spread and even persist, HGT could facilitate their transmission to non-target species. Worryingly, this risk remains poorly documented and characterized in current gene drive risk assessment frameworks and largely ignored in the Target Species Complex model (12). Indeed, the latter, relying on the phylogenetic proximity and sexual compatibility, does not consider such a mechanism operating outside of sexual reproduction. Failing to incorporate HGT into risk assessments could result in the unintended spread of gene drive constructs beyond the intended species complex. This, therefore, reflects a critical blind spot in current governance and biosafety models.

Ethics and Oversight

Defining an entire species complex as the target sidesteps key ethical considerations, as it assumes that nonhuman organisms can be freely engineered and eliminated based solely on their genetic proximity to a target species. Such a perspective disregards intrinsic value of biodiversity, as well as local ecological knowledge and cultural perspectives, reducing complex ecological relationships to mere obstacles in the pursuit of vector control.

In other words, TSC emphasizes efficiency over biodiversity conservation and ecosystem preservation. Species complexes

are considered in a reductionist manner as convenient genetic conduits or delivery systems, rather than part of an ecosystem. The TSC prioritizes technological efficiency over responsible scientific stewardship and, in so doing, creates a dangerous regulatory loophole.

All this being said, it's important to acknowledge the pressing human health challenges that drive the search for effective interventions, particularly in malaria-endemic regions. The status quo is not an option, and clearly there's a need for action to address these incredibly harmful diseases, and this often means innovation.

But innovations should not come at the expense of responsible stewardship. Accurate species identification has been considered a central tenet of successful management, be it for agriculture pests (13, 14) or for disease vectors (15). The concept of the Target Species Complex risks diluting this cornerstone by shifting emphasis away from precise species-level identification. That could create a risky trend in vector control.

A truly responsible approach to gene drive technology techniques should prioritize precision, containment, reversibility, and intraspecies complex information, rather than broad, unchecked genetic alterations of entire species groups in the name of efficiency. Only by upholding these standards can researchers ensure that innovation is carried out responsibly.

ACKNOWLEDGMENTS. C.B. is grateful to Eva Sirinathsinghji for her insightful comments on a previous draft of this manuscript.

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