ETHICS OF GENE DRIVE MOSQUITOES FOR MALARIA ELIMINATION

ETHICAL ANALYSES CONCERNING THE DEVELOPMENT AND USE OF GENE DRIVE MODIFIED MOSQUITOES FOR MALARIA ELIMINATION

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Descriptive Note

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Lay Abstract

This thesis is concerned with presenting analyses regarding key ethical issues regarding and arising from the development and potential use of gene drive modified mosquitoes for the purpose of malaria elimination. Chapter one explores whether the development and use of this technology can be fairly considered unethical in principle; concluding it cannot be. Chapter two explores the appropriate relationship between this technology and the precautionary principle, a prominent regulatory and governance principle which has been invoked as ostensible support for an indefinite global moratorium on all gene drive technology. Chapter three articulates, expounds, and provides rationale for the ethical principles selected to guide stakeholder engagement by Target Malaria, one of the leading consortiums working on research and development of gene drive biotechnology for malaria control. Chapter four attempts to locate the ethically appropriate locus of political organization from which to seek permission for a gene drive modified organism release.

Abstract

This thesis is concerned with presenting analyses regarding key ethical issues regarding and arising from the development and potential use of gene drive modified mosquitoes for the purpose of malaria elimination. Each of the chapters constituting this thesis offers a rigorously researched analysis which attempts to answer questions thus far unanswered in the academic literature. Chapter one explores whether the development and use of this technology can be fairly considered unethical in principle; concluding it cannot be. Chapter two explores the appropriate relationship between this technology and the precautionary principle, a prominent regulatory and governance principle which has been invoked as ostensible support for an indefinite global moratorium on all gene drive technology. The chapter concludes that the precautionary principle, at least as articulated by UNESCO, does not provide justification for a global moratorium on gene drive technology. In fact, the precautionary principle is likely unfit as a regulatory norm for some kinds of gene drive products and purposes. Chapter three was co-authored with Delphine Thizy, Global Stakeholder Engagement Manager for Target Malaria, one of the leading consortiums working on research and development of gene drive biotechnology for malaria control. Together we articulate the ethical principles selected to guide Target Malaria's stakeholder engagement, as well as provide the rationale for their selection and expound upon some early lessons from their implementation. Chapter four offers an analysis with the goal of locating the ethically appropriate locus of political organization from which to seek permission for a gene drive modified organism release into the shared environment. The chapter considers the appropriateness of each of the following levels of political organization: consent of individuals, local communities, nation states, and international governance institutions. The conclusion arrived at, with some caveats, is that such a decision is most appropriately issued by a nation state.

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List of all Abbreviations and Symbols

AUDA-NEPAD: The African Union Development Agency

CBD: The United Nations Convention on Biological Diversity

COMEST: United Nations Educational, Scientific, and Cultural Organization's (UNESCO) World Commission on the Ethics of Scientific Knowledge and Technology

CRISPR: clustered regularly interspaced short palindromic repeats

CRT: cluster-randomized controlled trials

EGD: engineered gene drive

EGDO: engineered gene drive organism

GDMM: gene drive modified mosquitos

IEPI: Institute on Ethics and Policy for Innovation, McMaster University

IHR: International Health Regulations

MDA: mass drug administration

NASEM: U.S. National Academies of Sciences, Engineering, and Medicine

NGO: Non-governmental organization

PP: Precautionary Principle

UN: United Nations

UNESCO: The United Nations Educational, Scientific and Cultural Organization

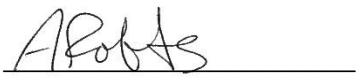
WAHO: West Africa Health Organization

WA-IVM: West Africa Integrated Vector Management

WHO: The World Health Organization

Declaration of Academic Achievement

I, Aaron J. Roberts, do hereby declare that this thesis entitled ETHICAL ANALYSES CONCERNING THE DEVELOPMENT AND USE OF GENE DRIVE MODIFIED MOSQUITOES FOR MALARIA ELIMINATION is an original work authored by me towards completion of the requirements of the award of the degree Doctor of Philosophy in the Department of Philosophy, McMaster University, Hamilton, Ontario, Canada. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.



Signature

17 October 2022

Date

Thesis Introduction:

This PhD thesis is primarily constituted by a series of applied ethics analyses meant to inform policy and governance deliberations relating to the development and use of engineered gene drive applications in mosquitoes for malaria elimination. Focus is given to gene drive research and development work being done for malaria elimination on the African continent. Of note regarding the structure of this thesis; it is what McMaster University's School of Graduate Studies terms a "sandwich thesis", which just means that each chapter of this thesis has been prepared as a standalone manuscript meant for individual publication in an academic peer-reviewed journal. There is not a singular question or overarching argument towards which all of the chapters of this thesis build as is usual in a more traditional monograph thesis. Rather, this thesis is more of an anthology of work which is thematically unified by an applied ethics analytical approach, and the purpose of providing analysis and synthesis towards informing policy formation and governance deliberations pertinent to the technology of gene drive modified mosquitoes in the context of its ongoing development. Because the chapters are written as standalone manuscripts, the reader will find that several of the pieces briefly cover very similar material in their introductions and/or background sections in order to familiarize the reader with gene drive technology and the relevance and importance of its potential for malaria elimination. Aside from this inescapable repetition of context setting, the analytical content and argumentative thread of each chapter is quite distinct from each of the others.

In terms of my research methodology, I began this work in 2017, just three years after the first public announcement of the discovery of an, as yet theoretical, genetic method which would allow for engineering of gene drive molecular mechanisms using the clustered regularly interspaced short palindromic repeats (CRISPR) gene editing technique (Esvelt et al. 2014); a technique which had itself been discovered only two years earlier in 2012. Though various forms of 'selfish' genetic mechanisms, or gene drives, had been explored and tinkered with before this time, progress had always been extremely slow, the available tools inefficient and imprecise, and the work never got very far nor presented great practical promise. CRISPR gene editing technology presented the first opportunity to engineer gene drive in a relatively fast, high precision, and economical manner. I began my research by attempting to locate all the relevant literature I could find on gene drive and ethics related to it through systematic review of scientific and academic publishing databases. Though there was already a significant and growing scientific literature available by which to become familiar with the technology of gene drive, there was a marked scarcity of publications regarding the ethics, policy, governance, or regulation of this brand new technology. Researchers were calling for the development of "societally acceptable rules of the road" (Adelman et al. 2017), and a trail blazing report published by the U.S. National Academies of Science, Engineering, and Medicine (NASEM) acknowledged the vital need for the development of ethics research and guidance regarding this powerful new technology (National Academies of Sciences, Engineering, and Medicine 2016).

In light of this limitation on my ability to systematically review a pre-existent and established scholarly discourse I had to find other ways to access and engage with the ethics discourse which was gradually emerging contemporaneously with my progress through the PhD program. Early on I set a Google Scholar alert for the search term "gene drive" which has for several years sent me almost daily email notifications regarding any scholarly publications indexed by Google Scholar which reference gene drive. I also subscribe to several email newsletters, notifications and digests which have become available within the gene drive scholarship and policy discourse space. And of course, as I proceeded through the work I conducted ad hoc literature searches on related and adjacent topics which were informative of my thinking along the way. But the opportunities which have offered the richest access and engagement with the ongoing conversation concerning gene drive ethics, policy, and governance have been afforded to me in my role as a Graduate Research Assistant at McMaster's Institute on Ethics and Policy for Innovation (IEPI). For instance, within this role I enjoy the opportunity to act as IEPI's representative to the Outreach Network for Gene Drive Research (genedrivenetwork.org), I joined delegations at international governance and policy forums such as proceedings of the UN's Convention on Biological Diversity, participated in several high-level technical briefings and bi-lateral engagements with representatives of various governments and regulators, presented and participated at numerous conferences and workshops regarding bioethics and gene drive policy and regulation, and helped plan and coordinate two panel discussion series on unsettled ethical issues in gene drive research involving international panelists with a diversity of expertise and perspectives, including participating on one of these panels as an

burgeoning expert myself. This level of immersion, networking, and participation in the global conversation taking place around how to approach the ethics, regulation, and governance of gene drive technology has granted me insight regarding which ethics questions are pressing and relevant for informing ongoing deliberations around policy and governance of gene drive technology.

By way of broad and general context setting for the analyses to come, I suppose it is worth first addressing the question: Why do gene drive modified mosquitoes for malaria elimination merit several in-depth applied ethics analyses? Ethics is the philosophical discipline of sorting right from wrong action. When faced with challenges in deciding when and how to act, careful ethical analysis of the broadest set of relevant considerations and available data can aid us to act rationally in service of our values. Well trodden scenarios of human action and activity have received thorough examination and arguably thousands of years of collective ethical analysis yielding several abstracted systems of normative thought and attendant principles and heuristics (variously appropriate for use at different levels of analytical resolution) for guiding action ethically. However, novel technologies grant humanity new avenues of action potential, and can pose challenges for integration or coherence with our familiar ethical principles and heuristics that were developed in a context which lacked the options for action afforded us by some novel technologies. The greater the power to affect change in the world a novel technology affords us, the more important it is for us to understand how the new opportunities for action a technology introduces ought to be integrated into our existing systems of ethical thinking. This integration requires careful ethical analysis of the novel technology, the context in, and

purposes for which it arises, and subsequent synthesis with existing systems of ethical thought and practice. Engineered gene drive is one such novel, and potentially extremely powerful, technology.

Gene drive is a phenomena in which a genetic element biases inheritance of a specific trait so that it is inherited by the offspring of the organism carrying a gene drive at greater than the Mendelian rate of 50:50 chance found most often in nature (Alphey et al. 2020). The phenomena of gene drive is not novel, it occurs naturally in the wild (Bier 2022). What is new is our ability to precisely and reliably engineer a gene drive molecular mechanism and combine it with the genetic trait we wish it to transmit inter-generationally, theoretically in any sexually reproducing species. Though this biotechnology remains untried outside proof-of-concepts contained in laboratories, it may afford humanity the ability to edit the genomes not only of individual organisms, but of entire species populations with a previously unseen precision and efficiency. One proposed application of engineered gene drive technology leading the field in development is in mosquitoes as genetic vector control for malaria elimination.

Malaria is a disease humanity has unhappily contended with for millennia, and which to this day causes over 200 million cases of morbidity and well over 400,000 deaths annually. Approximately 90% of this disease burden is carried by people living in Africa, and approximately 70% of these deaths are of children under the age of five years (“World Malaria Report 2021” 2021). Remarkably, these numbers represent enormous progress towards malaria elimination, halving numbers from just a couple of decades earlier. However, progress has stalled and even begun to backslide since

2016. Our existing tools for fighting malaria, anti-malarial drugs and insecticides, are losing efficacy as their targets, the plasmodium parasite which causes malarial disease and the mosquitoes which act as vectors and incubators for the parasite, continually evolve resistance to them. If we are to maintain the progress we have made, let alone make further progress in the fight to eliminate malaria, we need new tools (World Health Organization 2020).

Enter gene drive modified mosquitoes for malaria elimination. We have malaria; a pressing health crisis in need of novel tools, and engineered gene drive; a powerful novel biotechnology which holds great promise for the new opportunities it would grant humanity in terms of enacting relatively precise, effective, efficient, and economical changes to a disease vectoring insect population, thereby ameliorating or even ending the malaria health crisis. There are over 3,200 species of mosquito and only a tiny fraction of them vector malaria. One species in particular, *Anopheles gambiae*, which is exclusively endemic to the continent of Africa, is responsible for vectoring the majority of malaria. There are multiple versions of gene drive technology being developed to be leveraged to reduce or remove the harm currently caused by *Anopheles gambiae* and its harmful vectoring of malaria (Bier 2022). One method is referred to as a suppression drive and is designed to cause a severe decline or even total collapse in the target population, for instance by causing all offspring of the introduced gene drive organisms to be male, thus lowering the ratio of females in the population with each successive generation, thus lowering the population's ability to maintain a sustainable rate of replacement. Another kind of drive is called a modification drive. This kind of drive aims to cause a population-wide genetic

alteration which makes it impossible for the plasmodium parasite which causes malaria to incubate and subsequently be vectored by any *Anopheles gambiae* carrying the drive mechanism. This method alters a species population to remove a targeted harmful genetic trait (e.g. the ability to incubate and spread malaria), but leaves the species population in its biological niche, though permanently genetically altered.

Because it is powerful, new, and untried (not to mention, because it involves genetic engineering) this technology is attended by uncertainty, distrust, and fear. Many ethical questions yet surround this technology, and until we have faced, philosophically contended with, and contextualized them we cannot proceed responsibly towards field testing and potential release. Some ethics questions raised regarding the technology include: Is engineering gene drive unethical in principle? Even if it is not, gene drive has potential to be a very powerful and ecologically disruptive technology. Would acting in accordance with the precautionary principle require that we place a global moratorium on all engineered gene drive field testing? If we were to proceed with field testing, what ethical principles should guide community and stakeholder engagement practices? Who, or what level of political organization, holds ethically justified authority to grant or withhold authorization for release of gene drive modified organisms into the shared environment? These are the questions I sought clarity around over the course of my research and analysis. To each of these questions I dedicated a chapter of this thesis. Since each chapter is written as a standalone manuscript, I have written a brief preface for each to provide context, elaborated rationale for the particular analysis, and some narrative connection with the rest of the thesis.

Preface to Chapter One – Is engineered gene drive technology unethical in principle?

In this chapter I examine the question of whether engineered gene drive technology is unethical in principle. This is the most philosophically abstract of the four pieces which make up this thesis anthology. Given the more ontologically and epistemologically fundamental subject matter I wade into here, it is likely also the most controversial or polarizing since in this piece I defend the idea, through appeal to public reason considerations, that there are justified bounds on the kinds of considerations it is appropriate to entertain as serious contributions to political deliberations around the development and potential use of gene drive technology. There is a notable scarcity of literature addressing fundamental ideological, or axiomatic, opposition to gene drive technology despite there being significant opposition of this kind, including at high political levels and fora of policy and governance deliberation. Perhaps there are many who agree with me that opposition of this kind cannot be engaged with usefully and constructively; perhaps this is the reason for the absence of scholarly discourse on the subject? Regardless, if ideologically opposed views are not being directly engaged in the literature, I believe there should at least be an explicit account defending why this is the case and why it is justified to be so. While I make no claim that the account I offer here should be the only, final, or authoritative version of such an account, I think it is one way of justifying the drawing of a proverbial ‘line in the sand’ between democratically useful and not useful deliberative discourse around the subject of policy and governance for engineered gene drive technology.

Chapter One – Is engineered gene drive technology unethical in principle?

1. Introduction

What does it mean for a type of action to be unethical 'in principle'? I take it to mean that in any and every instance, a type of action defined as unethical in principle commits a wrong, irrespective of context. Research and development of engineered gene drive (EGD) technology is a category of action (or collective set of actions) being called into question along these lines – is it unethical in principle? Some vocal detractors claim or strongly imply that it is, and they consequently advocate for regulatory policy in line with this belief – several going so far as to call for an indefinite global moratorium on continued research into EGD technology, particularly if that research would involve release of EGD organisms outside of a lab environment ("Europäisches Parlament Fordert Verbot Der Freisetzung von Gene Drive Organismen," 2021; *Texts Adopted - COP15 to the Convention on Biological Diversity (Kunming 2020) - Thursday, 16 January 2020*, 2020; Foote, 2020; Herren et al., n.d.).

In this essay, I explore a circumscribed answer to this question. Namely, I consider whether there are any publicly justifiable reasons for holding that EGD is unethical in principle. It is my aim to show that the in principle ethical qualms some critics raise regarding the nature of EGD applications are unaligned with publicly available normative concerns. Several arguments are commonly leveraged to support the position that EGD technology development and use is unethical in principle, but they boil down to the charge of human hubris understood in relation to humanity's

appropriate relationship to nature – either intrinsically or extrinsically.[1] This includes related claims that EGD technology is unethical in principle on the grounds that it would harm or destroy intrinsically or extrinsically valuable aspects of nature. I will argue that holding the position that EGD is unethical in principle depends on believing some highly controversial premises.

Such an argument could be made in one of at least two ways. Assuming nature or certain of its aspects do hold intrinsic value, one available avenue of argumentation would be to point out there are no arguments made by the critics of EGD technology which describe how use of EGD technology would harm or destroy this ostensibly present intrinsic value. From a public reasons perspective, it might be additionally argued that such a description, at least one which is made on the basis of public reasons, is unavailable since we have no epistemic access to knowledge of the existence or features of this intrinsic value of nature which critics claim exists and use of EGD technology would somehow harm. So essentially, the response to the critics would be, "How do you know?" However, I think there is an argument available which more fundamentally undermines the claim that 'EGD is unethical in principle because it would harm or undermine the intrinsic value of nature'. That is, to argue that intrinsic value exists only within subjectively experiencing entities for themselves, and even supposing nature is such an entity, and therefore there is intrinsic value in nature, this still cannot create in principle ethical reasons against human intervention

[1] Ronald Sandler has explained elsewhere why neither deontological normative theories nor indirect consequentialist normative theories would support the view that using an EGD technology is unethical in principle (Sandler, 2019). I explore here a different vein of argument which relies on the claim of hubris.

upon nature, or aspects of it, if we can thereby reasonably expect to sustainably improve our own state of flourishing.

Recognizing that the bulk of my arguments will likely fail to persuade all readers, I close with an appeal to those who maintain that EGD is unethical in principle. My argument being that even if one views EGD as unethical in principle, one still has reason to support its use in some circumstances, such as for malaria vector control, given that EGD seems likely to be the lesser of two evils given the tragic harms caused by the status quo circumstances of malaria-caused morbidity and mortality. Subsequently, the position is even less defensible if the claim is that the prima facie wrong of EGD technology is not undercut or defeated by considerations of protecting and promoting human flourishing.

2. Hubris

Organizations such as Synbiowatch, ETC Group, and Friends of the Earth are civil society groups which advocate, at numerous governance and policy fora and in various reports and articles they publish, for the cessation of genetic engineering of all kinds ("Europäisches Parlament Fordert Verbot Der Freisetzung von Gene Drive Organismen," 2021; *Gene Drives*, n.d.; *Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13*, 2016, p. 160; *Reckless Driving*, 2016; *Texts Adopted - COP15 to the Convention on Biological Diversity (Kunming 2020) - Thursday, 16 January 2020*, 2020; Foote, 2020; Herren et al., n.d.; Synbiowatch, 2016). They have made various arguments in favour of instituting a global moratorium on research and development of EGD technology (*Over 160 Organizations Called for*

Moratorium on Gene Drives at the COP 13, 2016). Many of their arguments have to do with concerns around justice, balancing benefits and burdens, and worries around risk and safety. These are legitimate concerns about the ethics of *how* gene drive technology research might proceed and potentially be developed into applications, and they deserve appropriately thorough consideration. However, there is another vein of argument woven through their work, only sometimes explicit but very often implicit, which includes objections to the very concept of an engineered gene drive; to the method of genetic engineering itself. This theme arises in pieces with titles like *Gene Drives: Solution or Problem? Sacred or Synthetic?* (*Gene Drives*, n.d.), and *Reckless Driving: Gene drives and the end of nature* (*Reckless Driving*, 2016) in which the claim is made that, "Gene drives will change the fundamental relationship between humanity and the natural world forever." And which called synthetic gene drive the "omnipotent power to control nature" (*Reckless Driving*, 2016). While these claims do not always explicitly add the further statement that this is morally objectionable, it is strongly implied by both the tone and ostensible purpose of the documents – to stop gene drive research. This line of argument suggests that there would be something fundamentally morally transgressive or unethical about development and use of EGD technology. I suggest that these arguments boil down to the charge of hubris.

The concept of hubris comes to us from the ancient Greeks via a school of thought called virtue ethics and describes a dangerous overconfidence in one's abilities. Daniel Callies briefly addressed the question of whether research into EGD technology is rightfully considered hubristic in his essay "The ethical landscape of gene drive research" (Callies, 2019). He divides charges of hubris into two categories:

intrinsic and extrinsic. A charge of hubris could be considered an intrinsic objection to the technology on the basis that it displays an inappropriate attitude for humans to *even seek* the kind or level of power to influence and alter the genomes of entire species populations regardless of the positive or negative outcomes such actions might yield. Actions deigned inappropriate in this way are also sometimes derogatorily described as "playing God". To make a charge of intrinsic hubris one must hold that there is an appropriate and bounded relationship between humans and the rest of the natural world, and that engaging in EGD research and development transgresses that boundary. The predicted negative consequences of EGD research and development are at the heart of the second category of hubris – extrinsic hubris. The charge of extrinsic hubris claims that it is dangerously overconfident to think we could successfully harness the power of gene drive without causing serious unforeseen side effects, or even cause the 'end of nature'. Put another way, it is extrinsic hubris to act in powerfully consequential ways from a position of ignorance or naiveté. I consider here whether either category of hubris supports the judgement that EGD research and development is unethical in principle.

2.1. Intrinsic hubris: Violating the appropriate relationship with nature

Some detractors of EGD technology would have us believe that pursuing this technology places us in an inappropriate relationship with nature – that we overstep our proper bounds of action and influence. But claims of this kind raise the question; by what standard should we measure the appropriateness or inappropriateness of our relationship with and actions upon the rest of Earth's biosphere? Claims that EGD

technology would place us in such an inappropriate relationship come in different flavours. Ultimately, they are informed by one's fundamental axioms and frame of reference for final value. If one's axioms are primarily informed, for instance, by a Judeo-Christian-Islamic religion – i.e. via belief in some conception of an all-knowing, omnipotent, creator God who is of sole final value and source of all purpose – the charge of hubris tends to take the form that it is wrong to 'tamper' with the genomes of living beings in intentional ways since these kinds of actions fall within God's exclusive jurisdiction, and are not meant for humans. God has a plan, he designed all the creatures of the world to be the way he intended, and it is not for us to change or alter God's creation. By developing or using EGD technology we would change our fundamental relationship to nature, stepping beyond the bounds God intended.

Another flavour of this charge comes from environmentalist philosophies, such as Deep Ecology, and takes the following form – humans, along with all organisms, are part of nature and are best understood as not separate from, but as "knots" in the biospherical net of being; our identities are characterized via our relationships with the rest of the planet's biota (Næss, 2005). Axioms on this worldview acknowledge humanity's inclusion within nature but presuppose bounds on appropriate ways of being in relationship with the rest of nature since, on their account, every other organism has identical rights to live and pursue their interests that humans have. These are often rooted in claims about the intrinsic value of non-human organisms, and even non-living aspects of nature such as mountains and rivers; or holistic conceptions of Nature itself as being of final value and source of all purpose. Views of this kind make a similar leap of faith to those of religious ones because they rely upon a presupposed

external frame of reference for assessing value and assigning ethical demands consistent with this presupposition.

These two examples in no way exhaust all the ways similar reasoning takes place, rather they illustrate a problematic manner of reasoning for deliberations pertaining to public policy and governance. Arguments grounded in such worldviews rest on highly controversial premises and should be considered with appropriate scepticism. A charge of intrinsic hubris against EGD technology based on a worldview which presupposes, without publicly available evidence, an external frame of reference by which to assess action-orienting final value and subsequently derived 'appropriate' constraints on the scope of human action is a very shaky foundation upon which to base public policy and regulations.

Where then can we draw publicly available normative reasons for policy and regulation of EGD technology? Rather than presupposing an external frame of reference (e.g., God, or predetermined ideas about nature's telos), we should restrict our claims of fact about our ethical obligations to considerations available within a naturalized epistemology, a la Quine and Kornblith (Kornblith, 2002; W. V. Quine, 1995; W. V. O. Quine, 1992). After all, everyone "has pragmatic reasons to favor a cognitive system which is effective in generating truths" (Kornblith, 2002, p. 156). Our public deliberations ought to be grounded in what we can derive from evidence discovered via intersubjectively verifiable means – i.e. empirical means.

The idea that we can transgress or step beyond our appropriate relationship to nature relies on there being some real ontological distinction between nature and humanity; that we do or could exist separated from, or meaningfully outside of nature;

or that nature has an overarching purpose we are ethically obliged to consciously choose to align with. But how could this be? Humans neither exist, nor have origins outside of the same natural world we so often speak as if we are separate from. We know from Darwin (Darwin & Huxley, 2003), and an enormous amount of subsequent evidence derived via scientific observation, that humans have evolved from and alongside the rest of nature. Our actions and products are no less natural to creatures such as we are than the making of hives and honey to bees, and beaver dams and lodges to beavers. Certainly, we are capable of a far greater variety and ongoing variability of behaviour and production, but that does not make any of it less natural to humankind. We use the terms 'synthetic', 'engineered', and 'artificial' to delineate products of our shaping in contrast to the rest of the natural world. These distinctions are conceptually useful, but they do not parse an ontological difference. Rather, they denote a subcategory of natural things which have reached their current form and/or context by a causal path which included some degree of human influence. Humans cannot create *ex nihilo*, we can only remix what already exists within the bounds of natural physical laws. We are aspects of nature's causal unfolding which in our process of unfolding affect adjacent aspects of nature's unfolding. We have no epistemic access to an overarching grand purpose, telos, or end-goal of nature or god, so how could we begin to consciously align with such a thing?

The idea that natural and synthetic are mutually exclusive concepts, or that synthetic methods or products corrupt nature is incoherent since it would mean that nature corrupts itself. If possible, what would this even mean? No doubt nature changes; evolves, but by what standard can it be considered corrupt or not corrupt if its

own processes can corrupt themselves? Wouldn't this logically require that nature is innately corrupt to begin with? It seems such a claim requires evidence of some telos bestowed upon nature from an external frame of reference, and only from this frame could you judge whether it had been corrupted. But this external frame of reference (e.g., a creator-god's point of view) is precisely what I'm denying we have any empirical reasons for believing in, let alone knowing such a being's purpose/will/role/capabilities/relationship to morality.

There are unknowns (likely unknowables) beyond our epistemic reach. But anything or nothing might exist there, and we cannot make public policy based on the haphazardly supposed existence of a hostile unicorn army amassing on the dark side of the moon any more than we can the presupposition of a god, or gods, or whatever external frame of reference we may conjure to justify the normative claim that each of us should be moved by further unfounded claims that we have a bounded ontologically or teleologically appropriate relationship with our environment.

In the most foundational epistemic sense, all any of us has as the basis for our decision making is one's own personal phenomenological experience. It is the most epistemically fundamental bedrock of our reality – the most undeniable level, as it constitutes immediacy of experience. As Quine pointed out, "This is a prime specimen of naturalized epistemology, for it is a finding of natural science itself, however fallible, that our information about the world comes only through the impact of our sensory receptors. And still the point is normative, warning us against telepaths and soothsayers." (W. V. O. Quine, 1992, p. 19) We must build any public morality and ethics upon a network of intersubjectivity between each of our nodes of subjective

experience if we are to be able to make rational appeals to each other. We need to start from a place of looking out from our subjective experiential perspectives and building agreement about what exists beyond ourselves.

Reliance upon facts derived via the scientific method is the most reliable, epistemically available, and provable-to-others way of achieving this mutual agreement. It is a method by which we can show others our evidence and reasons for the conclusions we arrive at by it. Science (if it is truly science) shows its work, not just an answer with appeals to revelation, intuition, or other epistemically inaccessible 'reasons'. And science works relatively reliably! The scientific method works as our most accurate means to predict and effect specific causal outcomes. We have all the technological marvels of the contemporary world – commercial flight, smart phones, modern medicine, and agriculture, etc. – as evidence of this claim.

Scientific experiment and observation are also the means by which we have discovered the biosphere-wide disruptions that aspects of our modern way of life have imposed upon environmental systems we rely upon for our own continued wellbeing. No doubt, science is imperfect and susceptible to errors and bias due to the fact that it is a product of our epistemically limited subjective points of view, but by practicing it together we achieve the closest thing to objectivity available to us; inter-subjective agreement. Thus, claims grounded in non-empirically derived worldviews are less epistemically trustworthy because they cannot demonstrate mutually epistemically available evidence for their claims. Though the matter of whether a naturalized normative epistemology can tell us what to value is controversial, it is clearly the best method for coming to agreement about what the facts of the matter are. There is no

empirical/scientific evidence for the existence of an external final-value-imposing frame of reference. Valuation, it seems, must be sourced within a subjectivity, or at least it is only valuation of this kind we can justifiably claim epistemic access to.

Humans may now have the tools to influence and affect our environments and ecosystems to an unprecedented degree, but we remain inescapably within nature and its laws. They bound our actions and guide and structure our goals, if not to a singular path, then at least to a relatively narrow space of available options. We are part of nature, and everything we have done, do, or ever will be capable of is also necessarily an aspect of unfolding nature. We are fundamentally incapable of bringing about through our actions "the end of nature", and to suggest we could is misleading. Even taking a more constrained view of the concept of nature, for instance as the systems of living things on planet Earth, it is most implausible that any application of EGD technology could "end nature", even though uncareful release of EGD altered organisms may alter the trajectory of the Earth's living systems compared to circumstances which might result if we did not. The relevant question from my perspective is whether doing so would have net positive or negative effects on sustainable human flourishing, not whether it is our appropriate place to do so as judged in accord with a presupposed epistemically unavailable final-value-imposing frame of reference.

2.1.1 Gene drive's threat to the intrinsic value of nature

Even though, as argued above, we are inseparable from nature, and therefore cannot change our fundamental ontological relationship to it, might there still be a

reasonable argument that by using EGD technology we would violate some obligation of non-interference we owe the rest of the natural world? Is there some objective source of value or moral authority reference to which tells us something along the lines of "stay in your lane" regarding genetic engineering? One argument that could be made along these lines by critics of gene drive technology is that nature, or one or more aspects of it (e.g. a species of mosquito), are intrinsically valuable and that by developing and releasing gene drive organisms we would commit a wrong by altering or destroying intrinsically valuable aspects of nature. After all, even if nature is intrinsically valuable (as a whole or in it's parts), it is unclear why altering some aspect of it to be more beneficial to human flourishing would destroy or harm that which is intrinsically valuable in it. Before we accept the argument that the intrinsic value of nature is a legitimate barrier to ethical gene drive development and potential use, I suggest we interrogate the concept of intrinsic value and its relationship to nature to see whether it coherently does the justificatory work it appears to in this invocation.

Because I will be discussing some terms in this section which can be understood variously: value – intrinsic and extrinsic; final and instrumental – allow me to begin by presenting the way in which I mean them. I take value to exist only as a subjectively projected property. Something is valuable insofar as it is desirable to a conscious subject. So, a universe completely devoid of conscious, subjectively experiencing entities would by definition also be devoid of value. That is, by definition, no inanimate object, nor group of them, is capable of being intrinsically valuable nor valuable in itself. However, anything may have intrinsic *properties* which

can be considered valuable by a conscious, subjectively experiencing entity. For something to be intrinsic means that it exists within or as part of a thing. Therefore, intrinsic value is only that value which a conscious, subjectively experiencing entity reflexively projects upon itself – it values its own self-defined flourishing. This value can be said to be intrinsic to the entity since it exists only within and for itself. I take extrinsic value to be all remaining value; the kind of value a subjectivity projects onto anything or anyone outside of that one's self. All extrinsic value is also by definition instrumental value from the perspective of the valuer since it is done from the ground of a subjectivity which in a final recursive sense values itself and its own desire satisfaction finally and above all. This creates an interesting dynamic where subjective valuers (the only kind of valuers) can only value each other extrinsically and instrumentally since no subjective entities have direct experiential access to the subjective conscious experience of any other. This means that the intrinsic value – the reflexive self-valuation – of another subjective entity cannot itself create a reason for me to value it/them. For one entity (x) to be valuable to another (y) it must be extrinsically/instrumentally valuable to y in some way. Which is to say y projects value onto x when y perceives x can provide some kind of intermediary desire satisfaction – the ultimate and final goal for y always necessarily being y's own desire satisfaction. Valuation just is goal motivated orientation towards a thing perceived as beneficial to goal fulfillment / desire satisfaction. There seems to be no alternative manner of motivating a subjectively experiencing being other than some manner of desire satisfaction (or at least the perceived probability of it). The ways objects or entities can be extrinsically/instrumentally valuable are myriad. They may be useful,

or aesthetically pleasing, or nourishing, or a source of nostalgia, or of wonder, of friendship, love, etc.; they may have any desirous attribute or property.

The place I believe this analysis of the concept of value leads us is away from an unfortunate semantic conflation (which I believe leads some to a conceptual conflation) of 'intrinsic value' with 'intrinsic properties of a thing which are valued by a subjective entity'. This subsequently leads to an understanding that nature is not the kind of thing that can have intrinsic value unless it is a conscious, subjectively experiencing entity. And while there is no way to prove it is not, there is also no evidence, and therefore no reason to believe that it is. There are many aspects of nature which appear to be conscious, subjectively experiencing entities, humans being prime examples. Credible arguments can be made that all living things display evidence, or at least behaviours which indicate the possibility of, subjective experience. So, it may be the case that mosquitoes are intrinsically valuable – that is, each one is valuable to itself. However, even if this is true, this fact does not create a reason for me, or any other subjectively experiencing entity to value a mosquito, nor the whole lot of them. There may be all kinds of extrinsic and instrumental reasons to value mosquitoes; maybe one finds them beautiful, or fascinating, or attributes cultural significance to them, or consumes them for nourishment. Whatever the case may be, if a mosquito is valuable to you; if anything in nature outside of yourself is valuable to you, it is valuable extrinsically and instrumentally.

My reason for this exposition is to show why it is nonsensical to point to the intrinsic value of nature, or its aspects as a reason to protect and conserve it in its present state. Intrinsic value of a thing cannot in itself be a reason for some other

subject to value it because no subject has access to another subject's process of self-reflexive intrinsic valuation. All things outside of one's self can only be experienced, in some sense, as object.

This is not to say that we ought to treat other people as though they are mere means. We have good instrumental reasons to treat other people as ends in themselves, but the intrinsic/final value they ascribe to themselves cannot be a reason for me to ascribe final value to them from my perspective, but rather informs how I interact with them as I seek to promote mutually beneficial cooperation – since they are unlikely to cooperate with me unless it is also beneficial to themselves. But this instrumental motivation to treat others as ends in themselves only exists in circumstances when we require trust and cooperation with others to obtain our own desire fulfilment. Such circumstances arguably always exist in varying degrees amongst and between humans, especially in our very globalized world. But there are far fewer circumstances where this kind of cooperation is required or even possible between people and the rest of nature. No doubt we value many aspects of nature, and nature as a whole, but mutually conscious cooperation *per se* with nature or its non-human aspects is rarely if ever necessary for obtaining those benefits.

In the most foundational epistemic sense, the fact of the subjective phenomenology of consciousness – that each individual has only one point of view, unique and inaccessible to any other – must inform our most fundamental understanding of moral requirement. One's own subjective experience is the only source of intrinsic, and therefore final, value we each have epistemic access to. Many people believe, on the contrary, there exists a source of objective value or moral

authority in the universe which must intrinsically motivate ethical action towards others. However, if a source of objective value or moral authority exists, epistemic access to it so far is not available to us. Of course, even candidates for the source of objective value – God/s, Mother Nature, Gaia, etc. – are conceptually problematic sources of objective value since they raise the problem of the Euthyphro dilemma (Plato, 1963). That is, they seem to simply be a more powerful source of subjective value, not truly objective value. It is unclear then why even the existence of these things should give us intrinsic reasons for valuing in alignment with them. Though, such a power differential between us and them could give us an instrumental reason for doing so, if we had epistemic access to knowledge of the existence of such entities and what they value.

What follows from all of this is that it is not useful or epistemically justified to reference as justification for a public policy decision a presupposed external frame of reference, or entity which is a source of objective final value. The only thing the intrinsic value of which provides a reason for one to value it is one's self. This is the only intrinsic valuation anyone has direct epistemic access to. One's self is also the only thing one can value in a final sense since everything else one values is instrumental to the goal of one's own self-defined flourishing. Thus, in a final sense I can be motivated only by my own interests. I can value other people and things only instrumentally in various degrees of priority. I can, however, based on observation and reasoned inference, perceive that others also value themselves intrinsically and utilize this understanding as a basis for cooperating with them. This is the epistemic bedrock

we must build any moral justification from; some form of meta ethical psychological egoism (Shaver, 2021) appears epistemically unassailable.

Being deeply social creatures by nature, humans require social connections with our own kind to survive and flourish, and out of this need whole systems of morality, normative ethics, and culture have developed. But there is no basis by which these normative systems necessarily extend beyond our own species; at least no basis that cannot be reasonably doubted or disagreed with. The myriad and multitudinous non-human species we share the Earth with are many things to us. They are often a source of beauty and wonder; they can teach us through our observation of them about different modes of being and offer us an abundance of resources and ecosystem services upon which we humans rely, sometimes they are even become our companions. No doubt we rely on many of them both directly and indirectly in some form or another for an abundance of benefits. Meanwhile, we also compete with some of them for resources – as is the case with crop-eating pests. We are at times preyed upon by other species. Examples of human predators are far ranging, from tigers, to insects, to parasites, bacteria, and viruses. However, it seems clear that human flourishing does not rely on the conservation of each and every other species we share the planet with. For instance, it seems unquestionably a benefit to human flourishing that we were able to bring about the eradication of the smallpox, and rinderpest viruses. Without much controversy, programs to eradicate four other species causing disease in humans – Poliomyelitis (polio), yaws, Dracunculiasis (Guinea worm) and malaria – are underway (*Disease Eradication*, n.d.). While it is no doubt wise to avoid carelessly causing the extinction of other species as a general principle, there seems to

be no well-grounded, nor widely held, ethics principle which says we should never alter or eradicate another species. Rather it is only to the extent that ecosystems, and other species provide the instrumentally valuable resources and ecosystem services we rely on for our own flourishing, either directly or indirectly, that they are valuable to us. Within this internally sourced frame of understanding our behaviour towards other species can be immensely important from an ethical standpoint because their continued existence, and even the persistence of their current species-specific phenotype and behaviour, can be immensely important to us, and to other people important to us, whether directly, or indirectly. However, they are valuable to us extrinsically and instrumentally only, not in an intrinsic or final sense (even if they are finally and intrinsically valuable to themselves).

On this understanding, development or use of EGD technology cannot be in principle unethical due to its risk to intrinsic value in nature or its aspects. The intrinsic value of entities beyond ourselves do not create reasons for us to value them, and therefore cannot be reasons to protect them. This is not to say there cannot be reasons to protect and cherish nature and its aspects (there are so many reasons!), only that the reasons which remain for valuing these things are necessarily extrinsic and instrumental from our point of valuation, and therefore may be weighed in a cost-benefit analysis against each other. There is no incommensurate category of *for us* reason-generating intrinsic value out in nature. So genetic alteration or intentional extinction of a mosquito species via EGD cannot justifiably be claimed to be in principle unethical because of the intrinsic value of nature, nor of a species, nor of its

individual members. There may be other reasons to protect them, but their purported intrinsic value cannot reasonably be one of them for us.

2.2 Extrinsic hubris: Reckless overconfidence resulting in harm to nature

Charges of extrinsic hubris regarding EGD technology seem to boil down to concerns over insufficiently robust or informed risk assessment. This in itself is a fair and reasonable kind of concern but can in principle be ameliorated through continued scientific research to answer the relevant questions of empirical fact as thoroughly as is possible and/or reasonable. However, some add or imply the additional caveat that we should under no circumstances proceed with gene drive research, since in principle we cannot achieve a sufficiently robust or exhaustive risk assessment to justify proceeding – the ecological systems dynamics are too stochastic and complex to be able to intervene responsibly. This is a rather stronger claim, one that says we not only currently lack the knowledge necessary to responsibly release EGD organisms, but also the capacity for gaining that knowledge. This idea seems to be motivated by the fear that not only are there remaining known unknowns, which may become knowns through pursuit of further research, but also inevitably unknown unknowns, and naively stumbling into one of these might be our undoing.

The impulse to make the claim that gene drive is a ‘nature ending’ technology is perhaps understandable given that humanity is responsible for many, and ongoing, acts of destruction upon various aspects of the natural environment, including ecologies and many non-human life-forms. To make the charge of extrinsic hubris is to say that we may through our naiveté, ignorance, or recklessness cause changes to

Earth's environment and/or ecosystems in a manner that disrupts or prevents our future ability to flourish or perhaps even exist on planet Earth; or at least that the unknown unknowns we risk encountering are deserving of greater deliberative weight than the potential benefits we seek by way of EGD technology. No doubt there is ample evidence of past human activity which fits the description of extrinsic hubris to support these concerns. For instance, there is abundant evidence that human activity is responsible for the extinctions of hundreds, perhaps thousands of species (Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services, 2019) as well as being the primary cause of accelerated destabilizing climate change due to anthropogenic green house gas emissions leading to subsequent global warming (Cook et al., 2016). Many of us are rightfully troubled by these facts. To know that human activity is causing so much disruption to ecosystems and broader environmental systems upon which we rely, and to know as well that many of these harmful consequences are the result of reckless and/or willfully blind human decision making is extremely concerning. Knowing these disappointing and tragic facts about our historical failures and mistakes should certainly make us wary of making similar mistakes in the future, but they do not justify the claim that we cannot, and therefore should not try to, responsibly intervene in nature using EGD technology.

Humans rely on our environments and many aspects of the ecosystems within them for our own well being. They are the source of all the resources we rely upon to survive and flourish. If the environment on Earth were to stray too far from its current state in any of a multitude of ways, it could pose an existential risk to humankind. The preservation of natural systems in their current state, or recent states which we know

to have been supportive of our flourishing, is a good general baseline to prudentially aim at for preservation. And, as we are always finding new lessons to learn and resources to be gained from the wealth of Earth's biodiversity, the preservation of existing biodiversity is a wise strategic goal taken broadly; heuristically. This is especially true as we have historically operated largely from a standpoint of relative scientific ignorance regarding the intricate interactions which make up ecosystems, and with regard to our outsized power to influence fundamental changes and disruptions in those systems we rely upon, often indirectly, for our own well being.

It might be claimed that the use of EGD technology to suppress or genetically modify wild species populations risks causing irreparable harm to the environment and its ecosystems or food webs. Some go so far as to suggest the possibility of EGD-caused cascading collapse of nature's systems. It is a well understood truth that changes to one part of a system can result in changes to other parts of that system – this is to a large degree what makes something a system. Unless the grand system that is nature has a subjective experience of its own, a supposition we have no evidence to believe, then it cannot be harmed by changes made to it. Attribution of 'harm' requires a subjective point of view and attendant goals or interests, from which to understand it as such. It is nonetheless important to consider carefully how changes we make in the systems which we rely upon might affect us (as well as how they might affect other related systems which we also rely upon) and our prospects for continued flourishing, or even continued existence. Whether a change within a system is beneficial or harmful depends on one's subjective perspective from within the system. It is important to remember that currently, the existing system configuration is very

harmful in some respects to human flourishing. That is, the system we have does not appear optimized for us. And to the degree releasing EGD modified organisms risks changing the systems of nature in a manner which would further harm human flourishing, we have reason to be concerned. No doubt, changes which have a sufficiently high probability of bringing about such harms should be avoided, all else being equal. But to the best of our scientific reconning, it appears that careful employment of EGD technology could aid us in altering a number of sub-systems which are currently harmful to human flourishing (e.g. malaria vectoring mosquitoes (Roberts & Thizy, 2022)), or else on an unsustainable trend towards harmful destabilization (e.g. invasive rodents causing extinctions in fragile island ecosystems (Danielle Costantini, n.d.)). Prior to any release we should study the relevant eco-systems dynamics, have a comprehensive understanding of the genetic mechanisms at play, proceed in a stepwise manner considering safety, risk assessment, relevant regulations, and stakeholder engagement. All of this with the ultimate goal of promoting human flourishing. Taking all of these steps in advance of a release allows for a responsible decision to be made about whether and where to release a particular EGD application.

With that said, let us also acknowledge that humans have frequently, and often successfully, throughout our history made major changes to our environments, to our own patterns of behaviour, even to many other species at a genetic level through selective breeding for instance, without certainty of how the consequences would unfold. Dealing with uncertainty regarding the vast cascading consequences of our choices and actions is not a novel challenge. Nor is it one we can choose to avoid

given our innate epistemic limitations. We never have complete knowledge and control of a situation prior to deciding whether and how to act. Taking calculated risks which include acting without total certainty of all the effects of our actions is not only part of all innovation, but also a necessary and unavoidable part of living. So, it is unreasonable to demand a standard of certainty prior to choosing our actions, particularly when we face a tragic status quo, as we do in the case of vector-borne diseases and inadequate and failing tools for fighting them at this time in history (*World Malaria Report 2021*, 2021).

Though we may have achieved enormous influence in the processes of nature's unfolding on this planet, we are still within that unfolding. It is not within our power to corrupt, or end nature. However, it does appear to be within our power to influence and shape the unfolding of some particular processes of nature. We can and have sometimes done so recklessly in the past, thereby perhaps putting ourselves at existential risk by altering a process so that some relevant aspect of it falls outside of a parameter we require it to stay within for our own sustainable wellbeing. But we also can, and have done so after thorough research and planning in which we take a holistic view of the systems we depend upon and build an understanding of what changes we might make while maintaining the integrity of important aspects of those systems. So long as we act in ways that maintain or promote the aspects of nature's systems we rely upon so that they remain within parameters that allow our continued existence and flourishing on Earth given our requirements as a species, then I see no epistemically defensible further standard by which we could be said to have acted hubristically or

wrongly in relation to the rest of nature. As epistemically limited beings, we always must act in the face of some amount of uncertainty.

It's also not at all clear that humans flourish better in untrammelled, or 'more natural' environments. Our entire history, it could be argued, is a story of changing our environments and intervening on other living organisms to suit our needs and preferences. While we have made mistakes along the way (*The Cane Toad (Bufo Marinus) - Fact Sheet - DAWE*, n.d.), and there are ongoing human practices which are no doubt unsustainable long term ("Why We Need Sustainable Energy," 2012), overall there is a lot of evidence that humanity's interventions in nature, particularly in genetically modifying crops and livestock, first for thousands of years through selective breeding, now through genetic engineering, have yielded immense net benefits for human flourishing ("From Corgis to Corn," 2015). Virtually all the crops and livestock we cultivate have been heavily selected for by humans through countless generations of selective breeding. We may take a stumbling step backwards here and there along the way, but humanity's track record is actually very good when it comes to working out how to use bioengineering safely and beneficially. EGD technology appears to offer a powerful and promising toolset for performing some beneficial fine tuning of other species in our environment which at this time constitute an enormous ongoing threat to the flourishing and even survival of millions of people.

From a very big-picture, zoomed-out perspective nature and all its aspects may appear mutually harmonious; a grand self-balancing, self-sustaining system. However, look just about anywhere in that grand system's details through the millennia and aeons and you will find nature does not lack for enormous change over time (Rensing,

2020; Williams et al., 2019; Žárský et al., 2022). Endings and beginnings of system states, processes, and species blend into each other and occur again and again. Nature is not a steady-state system, and the changes it enacts and responds to are not always slow (*Dinosaur-Killing Asteroid Most Likely Struck in Spring*, 2022). While the principles that constrain its unfolding (i.e. the laws of physics) may remain static, the unfolding itself manifests as a dynamic, everchanging system which has only extremely recently in evolutionary terms brought about the species homo sapiens. There is no evidence of there ever having been a homeostatic, or permanently equilibrated state of nature that humans happened upon and disrupted. Belief in 'a natural state' contrasted with human disruption ignores not only the fact of humanity's inclusion within the category of nature, but also the dynamic changing nature of ecosystems which the fossil and geological record tell us existed prior to humans' evolution into a species and therefore independent of human influence. In fact, the fossil record provides convincing evidence that over 99% of all species which have ever lived went extinct before homo sapiens ever existed (Jablonski, 2004).

So, what is unethical, in principle, about even the most extreme hypothetical cases of engineered gene drive use; namely, permanently genetically altering a species or even causing its extinction? We can point to possible contextually based negative outcomes, but take the possible case where there are none from the standpoint of human flourishing, or they are far outweighed by positive trade-offs. What is special or precious about the continued existence of any given species in its current form, or at all for that matter? Certainly, the billions of years of natural history documented in the fossil record do not support the idea that, absent humans, nature protects and preserves

species, or that any kind of steady, equilibrated state of affairs is permanently maintained. Nature simply proceeds on its course of dynamic causal change in accord with its internal laws of physics. What sustained, fundamental aspect of nature or the natural world do we jeopardize with potential use of a human directed gene drive? Other species are valuable from a human perspective (the only perspective available to us to reason from) only insofar as they are valuable instrumentally to us, whether directly or indirectly. If a species existence or current genomic make-up is net harmful to humans, it would be better for us to change that in a manner which results in net benefit for humans. The greater the net harm to humanity caused by a species (directly or indirectly), the greater the degree of risk acceptable if removing or altering it would remove that harm.

While it remains debated by some whether unqualified good is a coherent concept, in consistency with all else I have defended here, it seems clear that what counts as 'good' can only ever truly be 'good *for*' a given subject in relation to its specific goals and interests. Given this subjective limitation we can value other species, biodiversity, and the environment instrumentally, but not finally. Nor can we hold other species in the same kind of value position as we do other humans. This is not to say humans are objectively more special or valuable, only to recognize that *we* happen to be human and therefore have innate subjective reasons to value ourselves and each other to a degree we do not have reasons to value other species. This is not said to condone cruelty or needless violence to other species, but rather to point out that we cannot be shown to bear ethical obligations towards other species on a level even approaching that which we do towards other humans. The higher priority of

value attributable to other human beings, as compared to non-human animals, is made apparent in the frequent, myriad, and direct ways our individual wellbeing depends on other humans and their positive (or at least neutral) regard towards us. As well, we each know what it subjectively feels like to be a human. We have intimate relationships with other humans. And it is in our nature to be social beings capable of complex social communication, cooperation, and reciprocity. It follows that the value we attribute to other humans seems deeper and more directly fundamental to our wellbeing, because it is.

Meanwhile, millions of other species have gone extinct, hundreds due directly or indirectly to human activity, and mostly this has little to no immediate, or in many cases even long-term, negative effects on human flourishing generally. In fact, some species extinctions have no doubt benefited humankind, for instance we may never have even chanced to evolve had the dinosaurs not gone extinct millions of years before the arrival of homo sapiens. The eradication of the smallpox virus was certainly a benefit to humanity. This is not always the case of course, the loss of some species would constitute a harm if, for instance we directly rely upon them for food, or for some other ecosystem service (e.g. bees and pollination), or they play some more indirect ecosystem stabilizing role (e.g. wolves in Yellowstone National Park(U.S. National Park Service, n.d.)). This raises the question though, is it species loss *per se* that concerns us, or is it the way that careless or unexamined actions on our part can arbitrarily cause extinctions of species which are integral to maintaining a certain ecological, and more broad environmental balance upon which our own flourishing, or even survival, depends? The latter seems more plausible to me.

There are over 3,200 recognized species of mosquito (*Culicidae - an Overview | ScienceDirect Topics*, n.d.), and only a handful of them vector the vast majority of malaria (Information et al., 2019). These few species are responsible for vectoring a deadly disease which causes nearly half a million human deaths, and over 200 million cases of infection and the resulting morbidity and suffering, *each year*. A disease which some claim is the single greatest cause of human mortality ever and which "…may have killed half of all the people that ever lived" (Whitfield, 2002). It is difficult to imagine one or even a handful of mosquito species providing an ecosystem benefit/necessity important enough to human flourishing to meet a threshold where it would, on balance, be more beneficial to maintain them in the ecosystem than eradicate or otherwise alter them in place to eliminate this enormous ongoing harm to human flourishing. Further, gene drive is a naturally occurring (in this instance I mean independent of human influence) mechanism which humans have discovered by observing nature. In addition to being neither unnatural, nor novel within nature, it is far more precise in its targeted effects than existing alternatives. Rather than blunt, imprecise tools for mosquito population suppression such as pesticide spraying or methods such as draining wetlands, both of which negatively affect species, ecosystems, and environments far beyond their targets, EGD technology would allow for precise, and far less ecologically disruptive, targeted beneficial alterations to species populations which in their current state are deeply harmful to humans. It is of course important that we ensure our experiments with this method are cautious, and that we carefully monitor the effects upon ecosystem processes brought about by human directed gene drives. Ethical goals always aim at sustainable human

flourishing. Our current circumstances with relation to vector borne diseases are severely deficient in providing large groups of people an environment in which they can safely flourish and utilizes methods which are both resource intensive and unsustainable. EGD applications offer promising solutions to some of these historically persistent impediments to human flourishing.

3. A moral appeal to those axiomatically opposed to engineered gene drive research

Some people hold worldviews which do not prioritize empiricism an rationality – e.g., axiomatically faith-based, eco-centric, or bio-centric views – and which may condemn the use of EGD technology as a sin or otherwise 'wrong' in principle via reference to a presupposed external frame of reference. However, contextual considerations may yet tip the ethical balance in the direction of supporting EGD technology development at least for certain applications. For instance, EGD applications show great promise as tools for the control and prevention of vector borne infectious diseases which are responsible for more than 700,000 deaths each year at current rates (*Vector-Borne Diseases*, n.d.). Malaria alone causes over 400 thousand human deaths annually, and over 200 million people suffer annually with the disease. Even granting that the use of EGD technology would constitute an in principle unethical act, is it more unethical than allowing millions of people to suffer and die while in possession of the means to develop effective tools to prevent all of that suffering and death? Without the existence of equally effective or promising alternatives, perhaps EGD could be viewed as a 'necessary evil' or 'lesser of two evils' by some of those who view it as wrong in principle. I present this line of

reasoning to suggest that even to those whose belief systems would label engineered gene drive as evil, perhaps if the tragic status quo context of vector-borne disease is taken into the equation, use of EGD applications may yet be understood as the lesser of two evils in some use cases where they could be instrumental in preventing an enormous amount of human suffering and death.

4. Conclusion

In this paper I set out to show that EGD research and/or implementation is not in principle unethical. We have no epistemic access to reasons for believing we owe our environment or ecosystems anything in a final sense, only instrumentally, in service of our own wellbeing. The universe is characterised by innumerable nested and multiply connected processes. Each of us, and humanity as a whole, arose out of and are inseparably part of that nexus of nested processes. Human behaviour and the products of it are not, cannot be, separate from nature. We were borne of nature and, as much as we enjoy nature's bounty of choice and opportunity, we yet inevitably live our lives bound by nature's inherent constraints. The universe (nature in its grandest sense) and life on Earth (nature in a rather more constrained sense of the word), will persist in some degree or form regardless of human action. Through our choices we may have some amount of influence upon how long humans will persist in nature. The processes which enjoy the longest and most sustainable existences are those which operate in relative sustained harmony with natural processes more powerful than they themselves are. Many practices humans engage in, or products of them, which have been thought of as unnatural, nature-destroying, or nature-corrupting, are processes that we have

experimented with and realized are unsustainable. They are unsustainable not to the continued unfolding of nature, but because they either directly, or indirectly threaten our own continued flourishing, or in some extreme cases even our continued existence. To the degree that we choose to employ unsustainable processes I believe it is fair to say we behave unethically, but not because we transgress against some external frame of moral reference (e.g., God, or otherwise-telos-imbued nature), nor because we 'harm' the environment or nature. Rather it is because whether directly, or indirectly, we harm ourselves. To some, this will appear a controversial perspective, but I believe it is the only conclusion we can fairly come to and expect reasonable agreement upon given the epistemological constraints placed on us by the fundamental limitations of subjective experience. I hope I have shown in the preceding there is nothing *in principle* wrong or harmful in the methods of EGD technology. No doubt such a powerful technology *could* be used in a way that *could* cause harm to my interests or those of other people but concerns along those lines exist contextually, contingently, and can only be answered through further research and ethical deliberation about the practical development pathway and implementation of this technology on a case by case basis (James et al., 2018). The countervailing consideration is that this powerful technology could be used with care to bring about immense benefits. What remains are questions of *under what circumstances* to use the technology, not *whether it is ever okay* to do so in principle. There are many questions and challenges along an EGD research pathway about how to go about testing and deploying appropriately designed gene drives, in ethically justified contexts. It is my hope that through continued cautious, careful, and stepwise research informed by public engagement and discourse,

we can arrive at ethically agreeable processes for developing, testing and potentially using EGD technology for applications which are sustainably beneficial to human flourishing.

Works Cited in Chapter One

Callies, D. E. (2019). The ethical landscape of gene drive research. *Bioethics*, *33*(9), 1091–1097. https://doi.org/10.1111/bioe.12640

Cook, J., Oreskes, N., Doran, P. T., Anderegg, W. R. L., Verheggen, B., Maibach, E. W., Carlton, J. S., Lewandowsky, S., Skuce, A. G., Green, S. A., Nuccitelli, D., Jacobs, P., Richardson, M., Winkler, B., Painting, R., & Rice, K. (2016). *Consensus on consensus: A synthesis of consensus estimates on human-caused global warming*. *11*(4), 048002. https://doi.org/10.1088/1748-9326/11/4/048002

Culicidae—An overview | ScienceDirect Topics. (n.d.). Retrieved November 12, 2021, from https://www-sciencedirect-com.libaccess.lib.mcmaster.ca/topics/agricultural-and-biological-sciences/culicidae

Danielle Costantini. (n.d.). *Examining Engagement: A Case Study on Gene Drive Mice and Island Biodiversity Conservation*. Retrieved May 29, 2020, from https://repository.lib.ncsu.edu/bitstream/handle/1840.20/37539/etd.pdf?sequence=1&isAllowed=y

Darwin, C., & Huxley, J. (2003). *The Origin of Species: 150th Anniversary Edition* (150th Anniversary ed. edition). Signet.

Dinosaur-killing asteroid most likely struck in spring. (2022, February 23). Science. https://www.nationalgeographic.com/science/article/dinosaur-killing-asteroid-most-likely-struck-in-spring

Disease Eradication: What Does It Take to Wipe out a Disease? (n.d.). ASM.Org. Retrieved June 17, 2022, from https://asm.org/Articles/2020/March/Disease-Eradication-What-Does-It-Take-to-Wipe-out

Europäisches Parlament fordert Verbot der Freisetzung von Gene Drive Organismen. (2021, June 9). *STOP GENE DRIVES*. https://www.stop-genedrives.eu/europaeisches-parlament-fordert-verbot-der-freisetzung-von-gene-drive-organismen/

Foote, N. (2020, July 3). NGOs call for moratorium on controversial "gene drive organisms." *Www.Euractiv.Com*. https://www.euractiv.com/section/health-consumers/news/ngos-call-for-moratorium-on-controversial-gene-drive-organisms/

From Corgis to Corn: A Brief Look at the Long History of GMO Technology. (2015, August 9). *Science in the News*. https://sitn.hms.harvard.edu/flash/2015/from-corgis-to-corn-a-brief-look-at-the-long-history-of-gmo-technology/

Gene Drives: Solution or Problem? Sacred or Synthetic? (n.d.). SynBioWatch. Retrieved January 24, 2021, from https://www.synbiowatch.org/gene-drives/

Herren, H., Mooney, P., Suzuki, D., & Ziegler, J. (n.d.). *A Call to Protect Food Systems from Genetic Extinction Technology: The Global Food and Agriculture Movement Says NO to Release of Gene Drives*. ETC Group.

Information, N. C. for B., Pike, U. S. N. L. of M. 8600 R., MD, B., & Usa, 20894. (2019). Malaria and related entomological and vector control concepts. In *Guidelines for Malaria Vector Control*. World Health Organization. http://www.ncbi.nlm.nih.gov/books/NBK538113/

Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. (2019). *Summary for policymakers of the global assessment report on biodiversity and ecosystem services*. IPBES. https://doi.org/10.5281/zenodo.3553579

Jablonski, D. (2004). Extinction: Past and present. *Nature*, *427*(6975), 589–589. https://doi.org/10.1038/427589a

James, S., Collins, F. H., Welkhoff, P. A., Emerson, C., Godfray, H. C. J., Gottlieb, M., Greenwood, B., Lindsay, S. W., Mbogo, C. M., Okumu, F. O., Quemada, H., Savadogo, M., Singh, J. A., Tountas, K. H., & Touré, Y. T. (2018). Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group. *The American Journal of Tropical Medicine and Hygiene*, *98*(6 Suppl), 1–49. https://doi.org/10.4269/ajtmh.18-0083

Kornblith, H. (2002). *Knowledge and its Place in Nature*. Oxford University Press.

Næss, A. (2005). *The Selected Works of Arne Naess: Deep ecology of wisdom*. Springer.

Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13. (2016, December 5). Friends of the Earth International. https://www.foei.org/news/friends-earth-international-160-organizations-called-moratorium-gene-drives-cop-13

Plato. (1963). *The trial and death of Socrates; Euthyphro, Apology, Crito, Phaedo*. London : Dent; New York : Dutton, [1963]. https://search.library.wisc.edu/catalog/999474853802121

Quine, W. V. (1995). Naturalism; Or, Living Within One's Means. *Dialectica*, *49*(2/4), 251–261.

Quine, W. V. O. (1992). *Pursuit of truth* (Rev. ed.). Harvard University Press.

Reckless Driving: Gene Drives and the End of Nature. (2016, September 1). ETC Group. http://www.etcgroup.org/content/reckless-driving-gene-drives-and-end-nature

Rensing, S. A. (2020). How Plants Conquered Land. *Cell*, *181*(5), 964–966. https://doi.org/10.1016/j.cell.2020.05.011

Roberts, A. J., & Thizy, D. (2022). Articulating ethical principles guiding Target Malaria's engagement strategy. *Malaria Journal*, *21*(1), 35. https://doi.org/10.1186/s12936-022-04062-4

Sandler, R. (2019). Should We Engineer Species in Order to Save Them? *Environmental Ethics*, *41*(3), 221–236. https://doi.org/10.5840/enviroethics201941323

Shaver, R. (2021). Egoism. In E. N. Zalta (Ed.), *The Stanford Encyclopedia of Philosophy* (Winter 2021). Metaphysics Research Lab, Stanford University. https://plato.stanford.edu/archives/win2021/entries/egoism/

Synbiowatch. (2016, July 28). *The Case for a Global Moratorium on Genetically-Engineered Gene Drives*. https://www.synbiowatch.org/gene-drives/gene-drives-moratorium/

Texts adopted—COP15 to the Convention on Biological Diversity (Kunming 2020)—Thursday, 16 January 2020. (2020, January 16). European Parliament. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0015_EN.html

The cane toad (Bufo marinus)—Fact sheet—DAWE. (n.d.). Retrieved June 17, 2022, from https://www.awe.gov.au/biosecurity-trade/invasive-species/publications/factsheet-cane-toad-bufo-marinus

U.S. National Park Service. (n.d.). *Wolf Restoration—Yellowstone National Park*. Retrieved November 12, 2021, from https://www.nps.gov/yell/learn/nature/wolf-restoration.htm

Vector-borne diseases. (n.d.). Retrieved December 24, 2021, from https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases

Whitfield, J. (2002). Portrait of a serial killer. *Nature*. https://doi.org/10.1038/news021001-6

Why We Need Sustainable Energy. (2012, December 15). *Science in the News*. https://sitn.hms.harvard.edu/flash/2012/why-sustainable/

Williams, J. J., Mills, B. J. W., & Lenton, T. M. (2019). A tectonically driven Ediacaran oxygenation event. *Nature Communications*, *10*, 2690. https://doi.org/10.1038/s41467-019-10286-x

World malaria report 2021. (2021). https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

Žárský, J., Žárský, V., Hanáček, M., & Žárský, V. (2022). Cryogenian Glacial Habitats as a Plant Terrestrialisation Cradle – The Origin of the Anydrophytes and Zygnematophyceae Split. *Frontiers in Plant Science*, *12*, 735020. https://doi.org/10.3389/fpls.2021.735020

Preface to Chapter Two – Reckless precaution: An analysis of the precautionary principle with reference to gene drive mosquitoes for malaria elimination

Having established in the previous chapter the reasons why I do not believe engineered gene drive is unethical in principle, I analyse here a different line of opposition regularly leveled at gene drive technology in an unqualified way; that it is just too risky and uncertain to try. In recent years in several forums of international governance, there have been regular calls and petitions made that a global moratorium be placed on environmental release of gene drive organisms, even for the purposes of nature conservation or public health research. These calls and petitions generally claim motivation and moral legitimacy through alignment with the precautionary principle. This is curious because it is not clear that the precautionary principle is aligned with the goals of these calls and petitions. In this paper, I forward an analysis of the precautionary principle with reference to the context of research and development of gene drive mosquitoes for the purpose of malaria elimination. Several arguments are provided for being skeptical that adherence to the precautionary principle should lead policymakers to instantiate a moratorium on all releases of gene drive organisms into the shared environment. I acknowledge there are many versions and interpretations of 'the' precautionary principle. However, if a global moratorium were to be instantiated it would most likely come about through United Nations (UN) processes, or those of its subsidiary bodies, such as the Convention on Biological Diversity (CBD) where several of these calls have been made. Therefore, this analysis is carried out with primary reference to the UNESCO working definition of the precautionary principle.

Chapter Two – Reckless precaution: An analysis of the precautionary principle with reference to gene drive mosquitoes for malaria elimination

1. Introduction

The precautionary principle (PP), also sometimes called the precautionary approach, is intended to be a deliberative referent or guide mechanism with the protection goal of steering decisional action away from options which might result in permanent harm to the natural environment and its systems and/or to intergenerational human health and equity. It is especially meant for application in cases where scientific evidence as to the suspected harm is inconclusive, yet sufficient scientific evidence exists that the harms are plausible. The PP is widely believed to have first been invoked in the 1970s when German lawmakers adopted a clean air act banning use of certain substances suspected in causing environmental damage even though evidence of their impact was inconclusive at that time (Stewart Brand, 2010). Since then the PP has become referenced and invoked with increasingly frequency in international legislation, in governance and policy fora, and by NGOs and environmental groups, to ensure prioritization of human and environmental wellbeing above less fundamentally important goals (e.g. purely economic considerations) (Hansson, 2020). This trend is particularly prevalent and influential in global governance fora such as the United Nations Convention on Biological Diversity (CBD), and the European Union (EU), though it also appears elsewhere.

CRISPR-based gene editing, a technique discovered within the last decade, is revolutionizing the field of genetic engineering, and has made development of engineered gene drive organisms (EGDO) practicable (Esvelt et al., 2014). Gene drive is the name given to a category of genetic mechanisms which increase the rate of

inheritance of a given genetic trait from 50% (Mendelian inheritance) to up to 100% in the progeny of a sexually reproducing organism (Burt, 2003, 2014). Gene drive can cause population-level proliferation of a genetic trait even if the trait in question confers a fitness cost. Thus EGDOs offer a means by which humans may make population or even species-wide genetic modifications by release of relatively few modified organisms into the environment (Burt, 2003, 2014). Gene drives do occur in nature, but only recently has their engineering and trait targeting by humans become practicable (Burt & Crisanti, 2018). EGDO constitute a novel category of biotechnology and have already attained lab-proven promise for a handful of applications (Scudellari, 2019; World Health Organization, 2014). However, no EGDO has been released into an open (non-laboratory) environment, even for testing purposes, at the time of writing. Thus, owing to the mixture of their powerful potential and untested novelty, the prospective release of EGDOs is attended by significant inherent uncertainty. Uncertainty not only regarding the success of these engineered gene drive organisms to fulfil their design purpose, but also regarding their safety for human populations and off-target effects on the environments into which they would be released.

Given the power of these technologies, their novelty, and the uncertainty which necessarily attends their prospective environmental release at this juncture, it is not *prima facie* surprising that the PP is repeatedly invoked as an appropriate principle for guiding governance of engineered gene drive research and products. Calls for regulations and binding international agreements which would govern gene drive research and applications in alignment with the PP come from both supporters and

detractors of continued research into engineered gene drive technology and its potential uses. Some view the PP as being compatible with continued gene drive research; including cautious, step-wise, responsible environmental release for testing purposes (James et al., 2018; World Health Organization, 2021). Invocation of the PP as aligned with moratorium on EGDO release is made particularly regularly by those who are inclined to view the technology as *too* risky (European Commission. Directorate General for the Environment. & University of the West of England (UWE). Science Communication Unit., 2017; Secretariat of the Convention on Biological Diversity, 2000; *Texts Adopted - COP15 to the Convention on Biological Diversity (Kunming 2020) - Thursday, 16 January 2020*, 2020). Many of the invocations of the PP by those who view gene drive as too risky are attended by claims that the PP would direct us to institute a global moratorium to prevent and/or halt all such research activities involving gene drive indefinitely ("Europäisches Parlament Fordert Verbot Der Freisetzung von Gene Drive Organismen," 2021; *Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13*, 2016; Foote, 2020; Herren et al., n.d.). Despite the frequency of the PP's invocation as a reason for moratorium on all potential gene drive environmental releases globally, arguments for why the PP should be interpreted to support a moratorium, if they are offered at all, generally lack nuance and overlook the need for case-by-case analysis. I have not yet discovered a persuasive account of why the PP should motivate us to such a strong and sweeping requirement as imposing an indefinite moratorium on not just a specific gene drive application, but upon the entire field of gene drive research and development across domains as disparate as public health, conservation, and

agriculture. These calls are particularly puzzling given that there is precedent and broad agreement in guidance and regulations from several respected governing bodies and organizations that synthetic biology technologies should be evaluated on a case-by-case basis (James et al., 2018; National Academies of Sciences, Engineering, and Medicine, 2016; Secretariat of the Convention on Biological Diversity, 2000; World Health Organization, 2021). Further, and of particular importance to this paper, one of the most prominent proposed use cases of gene drive technology is in mosquitoes for the purpose of malaria elimination, and this author questions whether the PP may be effectively or appropriately applied in this case at all.

This paper challenges the supposition that the PP provides us with reasons to prevent all research into engineered gene drive applications which would involve or require environmental release of gene drive organisms. Particularly, I focus on one, perhaps the most prominent, use case; that of research into engineered gene drive systems in *Anopheles gambiae* mosquito populations with the aim of contributing to elimination of malaria in Africa. I begin by introducing the UNESCO working definition of the PP and my reasons for selecting this articulation for primary reference in this paper. Subsequently, my first contention is that, though not explicitly so, the UNESCO working definition of the PP is substantively anthropocentric. Next, I argue that at least in the case of gene drive modified mosquitoes (GDMM) under development for malaria vector control, the PP is inappropriate for providing decisional guidance around whether to proceed with research involving GDMM field releases due to the tragic status quo circumstances caused by malaria. At a minimum though, the PP seems compatible with continued GDMM research and development

for malaria vector control. In case the reader believes I fail to make either of my first two arguments convincingly, I will also discuss the perceived uncertainty and environmental risks of proceeding with field releases of *Anopheles gambiae* GDMM, and point to evidence which indicates these risks do not rise to a level which should trigger the PP to direct instantiation of a global moratorium on gene drive research. Once I have laid out my arguments in defense of these claims, I will address some objections that might be lodged against them. If I am correct that the case of GDMM for malaria vector control provides at least one valid exception to the legitimacy of calls for a global moratorium on gene drive research involving field releases as motivated by the PP, then using the PP to categorically reject the use of gene drive will be shown to be invalid. This should bolster the already broadly (but not unanimously) agreed upon need for case-by-case assessment of gene drive technologies and their programs of research and development.

2. UNESCO's working definition of the Precautionary Principle

To begin, let us briefly examine the PP – its origins, history, and definition. The PP comes from the same conceptual lineage as age-old aphorisms such as 'better safe than sorry', and moral notions such as prudence, caution, and carefulness. The PP is intended as a refinement of these notions to make them more precisely targeted and articulated, and therefore amenable for application in the context of governance and policy decision making. The PP is envisioned as a decision-guiding principle to aid deliberating policy authorities in making ethically sound decisions by prioritizing consideration of more important and long-term variables; i.e. environmental

sustainability and inter-generational human well-being and justice. The PP is meant to be consulted particularly when normal risk assessment processes are confounded by matters which are attended by scientifically plausible, but uncertain harm; i.e. harm that cannot be presently confirmed with scientific evidence. Historically, the PP's application is most common in governance of innovative science and technology applications attended by uncertainty and major risk. Despite some evolution and refinement since it's initial legislative debut regarding air pollution in Germany in the 1970s (Stewart Brand, 2010), to date, the PP has no universally agreed upon definition or scope of application and is the subject of multiple interpretations as well as both extensive support, and numerous criticisms. While it is meant to guide decision making, it is not strictly speaking a rule, but rather more like a mechanism or procedural tool for deliberation. It is more accurate to think of the PP as the norm or normative structure that underpins various similar proprietary procedural tools for deliberation; different articulations coming from different governance and regulatory entities.

Subsequent to several slightly different articulations of the PP, in 2005 the United Nations Educational, Scientific, and Cultural Organization's (UNESCO) World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), upon mandate from UN member states, published an expert report on the PP – an attempt to find the common threads of the PP's historical usage and unify them into a single working definition to guide use of the PP for decision making in the UN and its subsidiary bodies. This definition is meant to facilitate a shared understanding of the PP which was becoming more commonly invoked and incorporated into international

governance documents and discussions, yet was undefined in any official way. While I expect this attempt at a universal definition has its detractors, I will make use of this version of the PP for the purposes of this essay given that it considers and aims to integrate the history of previous PP articulations, and because this paper considers the question of a global moratorium which, if established, would most likely come about through deliberations of the UN or one of its subsidiary entities (e.g. the Convention on Biological Diversity). The UNESCO COMEST report's working definition of the PP follows:

> When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm. *Morally unacceptable harm* refers to harm to humans or the environment that is
>
> - threatening to human life or health, or
> - serious and effectively irreversible, or
> - inequitable to present or future generations, or
> - imposed without adequate consideration of the human rights of those affected.
>
> The judgement of plausibility should be grounded in scientific analysis. Analysis should be ongoing so that chosen actions are subject to review. Uncertainty may apply to, but need not be limited to, causality or the bounds of the possible harm. Actions are interventions that are undertaken before harm occurs that seek to avoid or diminish the harm. Actions should be chosen that are proportional to the seriousness of the potential harm, with consideration of their positive and negative consequences, and with an assessment of the moral implications of both action and inaction. The choice of action should be the result of a participatory process.
> (World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005, p. 14)

I would like to begin analysis of the UNESCO working definition's relevance to the malaria elimination use case of GDMM by pointing out that on this definition, the PP tells us to avoid any activities that unduly risk the well-being of either 'humans or the environment'(World Commission on the Ethics of Scientific Knowledge and

Technology (COMEST), 2005) and not the environment alone. In other words, while the PP acts as a protectionist threshold condition meant to delineate permissibility, its protection goals relate not only to the environment, but also to humans. In fact, of the four qualifying clauses, only one could be interpreted to apply to the environment in addition to humans; the one specifying harms that are 'serious and effectively irreversible'. The rest focus exclusively on anthropocentric concerns; 'human life or health'; 'present or future generations'; 'human rights'. So even though this definition is formally logically disjunctive – applying to 'humans or the environment' – it is very substantively focussed upon the protection and wellbeing of human health, wellbeing, and intergenerational justice. Therefore, I would argue it is inappropriate to appeal to (at least UNESCO's articulation of) the PP to justify actions taken to prevent harm to the environment which would come at significant and permanent cost of harm to human populations since the UNESCO articulation (at least) equally protects humans. Whether one's value system grants priority of moral importance to humans or not, the PP is nowhere explicitly officially articulated to grant priority to environmental conservation over and above long-term human health and wellbeing. In the UNESCO articulation focus and substantive priority is explicitly given to considerations of present and future human welfare.

I point this out in order to suggest that fundamentally the PP is motivated by the value of protecting, in a broad and temporally far-sighted sense, the sustainable safety and flourishing of human beings. This no doubt includes protection of the environment's capacity to support human flourishing. Given this interpretation, the status quo context of global malaria incidence and the harm it causes to human health

now and in the future must weigh heavily in our deliberation by the lights of the PP about whether to proceed with GDMM research for malaria elimination involving field releases. Risk and uncertainty regarding ecosystem change or disruption must be considered and weighed alongside, and not independent of these concerns.

Given the elaboration above, I claim the UNESCO articulation of the PP is at least consistent with, if not explicitly and unarguably in support of, the following proposition (A): The PP would allow for – perhaps even encourage or require for the purposes of its stated anthropocentric protection considerations – the enaction of an available intervention which would significantly improve sustainable human health and well-being, so long as the foundations of environmental sustainability necessary for long term human health and well-being are not thereby irreparably harmed. If you accept proposition (A), then so long as research is carried out in a cautious and stepwise manner, GDMM under research and development for the purpose of malaria elimination would not trigger the protection mechanism of the PP as there is no scientifically plausible path by which GDMM would create catastrophic environmental collapse. Subsequently, invoking the PP as a reason to motivate an indefinite moratorium on this research is inappropriate. This also means invoking the PP as motivation for a categorical global moratorium on all engineered gene drive research involving gene drive organism environmental release is inappropriate since GDMM for malaria vector control provide a sufficient counter example to such a categorical global restriction. Acceptance of proposition (A) is not necessary for acceptance of the rest of my argument. However, if you agree with my claim that proposition (A) is consistent with the UNESCO working definition of the PP, which

amounts to an interpretation of anthropocentric moral prioritization as opposed to an eco-centric moral prioritization taken by some, you are likely to find the rest of my arguments superfluous, though they will further support a skeptical stance towards calls for a global moratorium on gene drive research.

3. PP inappropriate for application to gene drive mosquitoes for malaria vector control

Frequently the PP is invoked in cases where an exciting or profitable technology has come on the scene, and the benefits of the product's use must be weighed against the risk of plausible, but scientifically uncertain harm which may attend that use. For instance, the PP has historically been responsibly invoked to criticize and curtail the continued proliferation and use of asbestos when early scientific data, though inconclusive, and therefore uncertain, indicated that asbestos was having significant negative health effects on those exposed to it (Harremoës & European Environment Agency, 2001). According to the European Environment Agency, had the warnings regarding the hazardous nature of asbestos been headed earlier, as the PP would have guided us to do, hundreds of thousands of asbestos related cancer deaths and immeasurable human suffering could have been prevented (Harremoës & European Environment Agency, 2001).

The PP offers a reasonably consistent reminder and guidance to decision makers regarding when to avoid significant and uncertain risk in the interest of preserving a relatively safe and healthy status quo. It does so by highlighting a threshold of risk (i.e., scientifically plausible, irreparable harm to human or environmental wellbeing) which ought not be crossed, all else being equal. When the governance context for

which the PP is invoked to aid in ethical decision making involves a pre-existent baseline level of desirable, or at least acceptable, wellbeing for humans and/or the environment which may plausibly be irreparably harmed by the technology or product in question, the PP will dictate that we ought to prevent or otherwise cease the activity or product use which would engage such risks. In other words, the PP disallows risking irreparable harm for a potential benefit if an acceptable status quo exists. However, it is less clear what guidance the PP provides when the status quo is less than adequate; when it is attended by severe harms which the activity or product under investigation is intended to ameliorate. It seems reasonable to suggest, given the explicit goals and motivations provided in the UNESCO working definition of the PP, that it may be compatible with risking some minor harm to the environment, even some irreparable change if modest enough, for more substantial harm reduction in tragic or unjust status quo circumstances. On this interpretation the PP amounts to a threshold condition applicable only for the protection of an existing set of acceptable circumstances. After all the UNESCO working definition states, 'Actions should be chosen that are proportional to the seriousness of the potential harm, with consideration of their positive and negative consequences, and with an assessment of the moral implications of both action and inaction,'(World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005) indicating that inaction can also be inadvisable by the lights of the PP, and there can be no doubt as to the seriousness of the harm caused by status quo rates of malaria incidence.

To give the reader a sense of what is at stake in this case allow me to share a few statistics. At current global rates, on an annual basis, there are over 200 million cases

of malaria in humans, resulting in over 400 thousand human deaths (World Health Organization, 2020a). As difficult as those numbers are to accept, the truth is that they represent an enormous improvement over historical rates of malarial morbidity and mortality. Through significant ongoing investment and great international effort rates of malaria have declined substantially in recent decades and annual deaths from the disease have been cut in half since as recently as the year 2000. However, since 2016, not only has global progress towards malaria eradication stalled, it has begun to backslide (World Health Organization, 2020a). This is because the tools by which we have made progress in the recent past are beginning to fail us. The plasmodium parasite responsible for malarial disease continually develops resistance to our drugs, and the mosquitoes which vector the parasite continually develop resistance to our insecticides and larvicides causing a persistent decline in their efficacy (World Health Organization, 2020a). The World Health Organization (WHO), among others, have stated that the situation demands the development of novel complimentary tools if we are to maintain, let alone make progress on global malaria elimination (National Academies of Sciences, Engineering, and Medicine, 2016; World Health Organization, 2020b). This is the context in which we must judge the net risk introduced by GDMM, which evidence so far appears to indicate would be a very promising and affordable complimentary tool for controlling and suppressing ongoing malaria spread (Kyrou et al., 2018; North et al., 2020).

A position statement issued in 2020 by the WHO states that we need new tools to control malaria and thus must weigh benefits as well as harms in our evaluation of genetically modified mosquitoes (World Health Organization, 2020b). This language;

weighing *benefits* as well as harms, echoes the UNESCO working definition of the PP. There is no question there are possible use cases for engineered gene drive technology which would fit neatly into a paradigm of relatively easy PP application and interpretation. However, the malaria control and elimination use case is not one of them. As argued convincingly by Hansson, 'The precautionary principle cannot adjudicate between competing top priorities. In cases with such a priority structure, it may therefore have to be supplemented with decision principles suitable for weighing different potential outcomes against each other'(Hansson, 2020). The PP does not provide guidance when we are choosing between multiple options, each of which ostensibly aim at what is fundamentally better for reduction of long-term harm to humans and the promotion of circumstances for human flourishing. It may continue to remind us in these cases to pay attention to risks to the environment, but it cannot offer guidance on how to prioritize one or the other of these fundamentally important protection goals if the options available all involve trade offs between these top priorities.

Clearly, the status quo as regards malaria meets (and far surpasses) any threshold that might be established to claim it is 'threatening to human life and health' (World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005). No doubt this level of malaria incidence is 'serious' and every death which results from it is 'irreversible', as are the status quo circumstances causing those deaths given the nature and limitations of our current tools to lower malaria incidence. Additionally, around 70% of the aforementioned 400,000+ malaria-caused deaths are of African children under the age of five years (World Health Organization, 2020a).

So the cost in morbidity and mortality is not equitably distributed, not even close, making the current state of malaria spread and concentration deeply unjust and inequitable to present and future generations, in addition to being 'imposed without adequate consideration of the human rights of those affected' (World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005). All of this being the case, even if we find the PP is not well formulated to provide guidance in these circumstances since malaria is not primarily the result of human activities, it seems clear that the moral values underlying and motivating the PP (i.e. the value of sustainable, long-term, intergenerational human well-being and protection of the natural systems which support that well-being) ought to motivate us to take actions to avoid or diminish this existing harm whether the origin of that harm is human activity or not. This is to say, even if the PP does not provide additional reason to pursue GDMM research and development for malaria elimination, it is nonetheless compatible, based on its motivating moral commitments, with this work proceeding.

The PP might dissuade us from pursuing GDMMs for malaria elimination if existing tools were working, and not declining in efficacy, or we had comparatively powerful potential tools in development which involve less risk or uncertainty than GDMM that we could hold out just a little longer for – but this is not the case [2]. Every additional year we fail to develop and deploy effective new tools for malaria control

[2] In the late stages of editing this paper, the author became aware of early, small-scale vaccine trial data indicating A malaria vaccine has recently proved to be 77% effective in early trials and could be a major breakthrough against the disease. If this vaccine proves very efficacious, its existence may slightly weaken this argument as incidence of malarial disease may be greatly lessened through an alternative tool's use. However, GDMM remain a promising complimentary tool, and perhaps more affordably, and equitably accessible, as well as a more powerful tool as they may offer us a way to eradicate malaria altogether; a feat vaccines alone are unlikely to achieve as we have seen during the recent COVID-19 pandemic. A news article reporting on development of the vaccine in question can be found here: https://www.bbc.com/news/health-56858158

and elimination costs hundreds of thousands of human lives, and immeasurable human suffering. By taking all this context into consideration, understanding that the risk inherent in the status quo is far greater than the risk of careful testing of GDMM; which appear to be the most promising hope of remediating the tragedy of the malaria status quo, it becomes clear that we cannot morally afford to impose a moratorium on GDMM research for purposes of malaria elimination. In different, less dire and unjust circumstances the PP might justifiably incline us towards a moratorium (though these should always be qualified with concrete procedures and criteria for ending the moratorium) on use of a technology as powerful and as yet untested as GDMM, but the tragic extant malaria status quo must be accounted for in the moral calculus.

4. GDMM for malaria vector control and risk to the environment

Perhaps you do not agree with my arguments for interpreting the PP to be anthropocentric and therefore inappropriate or unhelpful to the task of guiding policy makers on the question of whether to permit continued research into GDMM for the purpose of malaria vector control. Even if your ethical orientation is eco-centric, or you otherwise interpret the PP's priority concern to be protection of environmental sustainability independent of consideration for human wellbeing, GDMM under development for malaria vector control and the attendant environmental risks should not trigger a PP motivated global moratorium on gene drive research. As GDMM are yet untested in an open environment, there is no doubt uncertainty about the precise nature and extent of the consequences (both intended and unintended) which might result from their release, even in a limited or controlled manner for the purpose of

testing as part of a responsible research pathway. However, while we cannot achieve certainty and precision in our knowledge regarding results until after field release testing has been conducted, we are not completely in the dark about what is likely to occur. To minimize uncertainty, we can draw on reasoning, experience of analogous circumstances, and scientific understanding of the ecosystems, organisms, and genetic mechanisms under investigation to make informed predictions about what is likely, or unlikely to happen if we release a given GDMM mosquito into the environment (Pearson et al., 2021). These empirical and analytical processes can yield a scope of scientifically plausible outcomes to inform governance and policy considerations. In fact, there are already guidance materials for testing genetically modified mosquitoes, including GDMM, published by trusted governance bodies (James et al., 2018; World Health Organization, 2021) and we have established methodologies for problem formulation and risk assessment (Connolly et al., 2021; Pearson et al., 2021; Teem et al., 2019). For instance Teem et al., and Connolly et al. have presented the results of a series of problem formulation workshops conducted with African scientists and regulators for potential GDMM environmental release. The paper by Connolly et al. in particular purports to present a comprehensive (though not exhaustive) analysis of 46 plausible pathways to causal chains of events which would be required for potential harms to occur. Their analysis revealed that,

> Most potential harms involved increased human (n = 13) or animal (n = 13) disease transmission, emphasizing the importance to subsequent stages of [environmental risk assessment] of data on vectorial capacity comparing transgenics to non-transgenics.
>
> (Connolly et al., 2021, p. 1)

This demonstrates that by engaging in the process of problem formulation we are able to identify plausible pathways to potential harm and conduct risk assessment and testing in contained environments to inform computer modelling so that once we are ready to test a given GDMM in the environment we have a lot of carefully gathered empirical data and informed predictions about what is likely to occur in the interactions between the GDMM and the rest of the ecosystem, including humans and other vectored diseases. Testing of GDMM in the environment would not proceed in advance of thorough investigation into all identifiable plausible risks and a scientifically informed conclusion that the release will not bring about net harm. In fact, James et al. advise that,

> …the safety standard for moving an investigational gene drive product from physical confinement to field testing should be a well-reasoned justification that it will do no more harm to human health than wild-type mosquitoes of the same genetic background and no more harm to the ecosystem than other conventional vector control interventions.
> (James et al., 2018, p. 15)

In terms of risk to biodiversity posed by GDMM release, in recent years many rigorous empirical studies have been conducted in order to estimate the environmental implications of removing *Anopheles gambiae* from their existing ecosystems. A recent comprehensive review of the existing literature by Collins et al has concluded:

> Anopheles gambiae is a species of importance because of its role as a vector of malaria, not as a key component of ecosystem food webs. […] Adult An. Gambiae mosquitoes are a relatively low-value, low-volume and disaggregated resource and this is reflected in a lack of evidence for any tight links with predators […] This generalist predation is a known stable strategy in ecological theory and contributes to dynamic equilibria in predator and prey populations and in the ecosystem in general. Several competing mosquito species could increase if An. gambiae density is reduced in specific habitats. Many generalist predators of An. gambiae already prey on these species and would substitute them for An. gambiae if the latter were less abundant. In this sense, any positive effects of

> competitive release on abundances of other mosquito species have the potential to compensate for any reduction of An. gambiae biomass in a diet.
> (Collins et al., 2019, p. 10)

All of this suggests that the strength of the empirical evidence supports the likelihood that heavily suppressing, or even causing the local extinction of *Anopheles gambiae* (a species of mosquito endemic exclusively to the African continent) would not cause severe ecosystem or food-web disruption.

As I hope you will have gathered, the scientific evidence points in the direction that there is much more harm to be mitigated by continued pursuit of GDMM research towards malaria vector control than there is risked by careful and stepwise research in line with published guidelines. While suppressing or eliminating *Anopheles gambiae* populations may have some off-target effects on the environment, there is no scientifically supported plausibility of permanent or catastrophic harm or degradation. Thus, even if the PP appears to you an appropriate and useful referent for making policy decisions around GDMM for malaria vector control, alignment with the PP does not require or suggest a global moratorium on gene drive research involving open field release.

5. Addressing possible objections to the PP's compatibility with GDMM for malaria elimination

An objection might be posed to my analysis that part of the UNESCO working definition of the PP states that 'Actions are interventions that are undertaken before harm occurs that seek to avoid or diminish the harm'(World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005). Since malaria has existed and has been causing harm to humans since time immemorial, the actions put

forward in the UNESCO definition of the PP are unavailable to us in terms of preventing the harm inherent in the malaria status quo situation. In response I would say, clearly we cannot prevent the immeasurable harm malarial disease has inflicted on human kind since time immemorial, but this fact does not preclude the possibility of our taking actions that could avoid or diminish future harm caused by the disease. 'Risk' can be defined as the product of the severity of a potential hazard multiplied by the probability of that hazard's occurrence (i.e. risk = severity of hazard x probability of hazard). If we weigh the risk, so defined, of further harm to humans in malaria status quo circumstances against the risk of environmental hazards posed by potential off target effects of GDMM, it seems uncontentious that the risk of human harm if we maintain the status quo is far higher than the risk of environmental disruption of careful, step-wise experimental release of GDMM which meanwhile appear to be a very promising new complementary tool in the fight to eliminate, or even eradicate malaria. While nothing in the future is ever truly certain, we know that the probability of similar levels of malaria-caused morbidity and mortality are very close to certain if we do not introduce effective new tools for reducing malaria incidence. Introducing new tools requires experimentation and testing as part of a responsible scientific development pathway (James et al., 2018). An engineered gene drive has been experimentally proven to be highly effective in *Anopheles gambiae* mosquito population suppression in a contained lab setting, even achieving complete population collapse (Kyrou et al., 2018). *Anopheles gambiae* is the species of mosquito responsible for vectoring the vast majority of Plasmodium falciparum, the primary malaria causing parasite, in Africa. This gives us scientific evidence that GDMM hold

powerful potential to be an effective tool of malaria vector population suppression, and resultingly of malaria incidence suppression; thereby providing us with a potential action to 'be taken to avoid or diminish that harm.'(World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005) This is what the PP advises is our moral duty.

This analysis is not incompatible with acknowledging uncertainty regarding the use of GDMM technology; that it is attended by some plausible risk of harm to the environment via ecosystem disruption. If this risk were the only one that needed to be considered, respecting the PP would very likely lead to a verdict that we ought to avoid environmental release of GDMM, even for testing purposes. But risk of environmental harm is not the only, nor is it the greatest risk we must consider in deciding whether to pursue GDMM technology for malaria elimination purposes. The far greater risk of harm to fellow human beings will result from a continuation of the status quo; from not pursuing promising novel tools for the purpose of malaria elimination, even if they are attended by some smaller amount of risk to the environment.

Elaboration provided in the UNESCO COMEST report on the PP would seem to further support my contentions on this point when they state,

> The PP is not based on 'zero risks' but aims to achieve lower or more acceptable risks or hazards. It is not based on anxiety or emotion, but is a rational decision rule, based in ethics, that aims to use the best of the 'systems sciences' of complex processes to make wiser decisions"
> (World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005, p. 16).

If we rationally weigh the risk of harm in the malaria status quo against the risk of harm due to GDMM environmental disruption, there is a powerful argument to be made that the former carries a far greater and more certain risk of harm than the latter.

As an additional aside, our existing tools for fighting malaria, such as insecticides and larvicides, have deleterious effects on the environment, yet we consider these acceptable side-effects given the benefits they offer us. It may be the case that GDMM offer us a tool in the fight to eliminate malaria which causes less harm to the environment than the tools we currently use.

6. Additional reasons the PP is an inappropriate justification for global moratorium on gene drive release

My argument for the interpretation of the PP as morally compatible with, but unhelpful in adjudicating, whether to proceed with GDMM research for applications to ameliorate the status quo regarding malaria is complete. Before closing I have just a couple more points to make about the inappropriateness of the way the PP has been invoked against engineered gene drive research and technology.

Firstly, invoking the PP as support for a globally enforced moratorium, for instance in the proceedings of the United Nations' (UN) Convention on Biological Diversity (CBD), is inappropriate based on the UN's own interpretation of the PP. The UNESCO report on the PP states,

> Countries choose their own level of acceptable risk and find their own balance between the PP and other issues and principles. Local circumstances may justify a deviation from the PP. For instance, regulations that allow the introduction of experimental new medicine for AIDS that have unknown but possibly deadly side effects, may not be considered to be in accordance with the PP, but for countries facing an AIDS epidemic that will kill many anyway, such an action can be justifiable. Implementation of the PP can vary from country to country because the chosen level of protection may vary, the socio-economic context is different, and priorities may differ.

> (World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), 2005, p. 43)

It is not difficult to see the parallels between AIDS and experimental medicines in the example above, and malaria and GDMM in the context of this essay. As has been pointed out, the tragic status quo of malaria incidence is not equitably distributed around the planet. A relatively small number of countries bear the overwhelming majority of malaria burden. UNESCO's articulation of the PP's appropriate scope would condemn the invocation of the PP by parties external to this context to call for a moratorium which would preclude heavily malaria-burdened countries and regions from deciding for themselves whether the uncertainty and risks posed by GDMM are worth the potential benefits they may bring. Thus, for this additional reason, it is inappropriate to invoke the PP to achieve a global moratorium on environmental release of all engineered gene drive organisms since the PP requires more localized context for appropriate application.

Finally, international moratoria or bans may be appropriate for specific products assessed on a case-by-case basis, but not for entire categories of scientific research, technologies, and methods in an unqualified manner as has been called for regarding engineered gene drive research. As already mentioned, there is broad agreement that genetically modified or edited organisms must be assessed not categorically, but on a case-by-case basis, and that therefore, while gene drive organisms may end up being assessed as overly risky for most use cases, if GDMM have a high likelihood of aiding us in eradicating malaria, particularly if we have no better or even equally promising alternative tools, then the moral values motivating the PP would seem to align with

continued pursuit of GDMM research, even involving environmental release, at least in the malaria elimination use case.

7. What then if not global moratorium?

As I hope it has become clear, if we take health and justice considerations into account alongside environmental concerns, the status quo regarding malaria is unacceptable. The PP can be interpreted as compatible with continued scientific pursuit including responsible, stepwise environmental release of GDMM for malaria vector control and elimination; even if it does not provide any additional guidance in this respect. As bioethicist Laurie Zoloth recently put it in her discussion of the same issue, 'Non-action is not safer, it simply makes the moral claim that our present situation is fine, safe enough, whereas it is actually morally unacceptable'(Zoloth, 2021, p. 1436). Policy makers therefore ought not invoke the PP with the goal of preserving our tragic status quo.

If the status quo is not okay, it leads one to ask what ought to be done about it. A reasonable answer is, we ought to do what can be done to help eliminate malaria. Moreover, we do it because when means and opportunity present themselves it creates a duty to rescue. Actually, according to Emerson and Singer, 'Three conditions must be satisfied to invoke a duty to rescue: there must be opportunity, capability, and the burden must not be so taxing as to make the circumstance before rescue preferable to the circumstance after rescue'(Emerson & Singer, 2010). The question remains: will GDMM provide the capability for achieving significant malaria elimination, or even eradication? Only further research involving field release of GDMM can inform an

answer to this question satisfactorily. For this reason, those in a position to make decisions around gene drive governance may be responsible in the sense of having a 'duty to rescue' (or at least a duty not to prevent rescue) to those currently living in malaria endemic locales. Those in a position of direct influence with regard to governance of gene drive technologies have both opportunity and capability to help or hinder development of GDMM tools for malaria elimination. Though some may believe it is contentious that GDMM for malaria elimination meets Emerson and Singer's last criterion, I contend it is not so contentious if the available scientific evidence is taken into consideration. Particularly if one attends closely to the degree of environmental risk purported by relevant scientific experts to be inherent to GDMM for the malaria elimination use case, to make the argument that results of careful pursuit of this technology's development are likely to be net negative, and thus a global moratorium is in order, seems at least naïve, if not wilfully blind. Meanwhile, there is significant promise, bolstered by proof-of-concept lab experiments, that rates of malarial morbidity and mortality could be reduced greatly by GDMM applications. The tragic malaria status quo should compel us to try.

8. Conclusion

Based on the articulation of the PP by UNESCO in their report on the principle, I have offered an interpretation that the PP is substantively anthropocentric and, while inappropriate for guiding a decision in this case, compatible with continued GDMM research, including careful and responsible field testing in the open environment. This is particularly because of the tragic status quo circumstances caused by malaria. If my

interpretation is valid, the PP cannot offer moral support for a blanket global moratorium on release of engineered gene drives into the environment. Rather, such deliberations should occur on a case-by-case basis considering both product and context of intended use. If the reader remains unpersuaded by my argument that the PP is substantively anthropocentric in its prioritization and is compatible, even primarily morally aligned, with continued GDMM research, the problem remains that the PP does not offer explicit guidance on how to prioritize between competing top priorities (e.g. long-term human health vs. environmental and ecosystem conservation). However, even on this understanding it seems impossible the PP should motivate the kind of moratorium under discussion. This is because the continually developing scientific evidence does not suggest the plausibility of fundamental and irreparable environmental harm resulting from continued GDMM research, even involving release. Further, in the case of research into GDMM for the purpose of malaria elimination, there are particularly compelling ethical reasons consistent with the moral goals orienting the PP, several of them explicitly stated in the UNESCO articulation, for pursuing continued research and development of GDMM for malaria elimination. In fact, particularly those who have positions of authority in governance of these technologies may have a duty to rescue (or at least not prevent rescue to) those living in the most malaria affected regions, even if that involves environmental release of GDMM, and even if such releases involve some uncertainty and risk of environmental disruption.

Considering all presented here I believe the conclusion stands that a nuanced understanding of the PP does not align with or support the legitimacy of calls for a

global moratorium on GDMM environmental releases for research towards novel effective tools for malaria elimination. Particularly regarding the African context, given the tragic status quo characterized by high and rising rates of preventable malaria-caused mortality and morbidity, invocation of the PP, predominantly by people in the global North, to prohibit even responsible development of one of the most promising malaria elimination tools appears myopic and morally misguided. In fact, these calls and petitions, and any decisions which align with them, are not cautious but in fact reckless with regards to human health, wellbeing, and intergenerational justice.

Works Cited for Chapter Two

Burt, A. (2003). Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proceedings of the Royal Society B: Biological Sciences*, *270*(1518), 921–928. https://doi.org/10.1098/rspb.2002.2319

Burt, A. (2014). Heritable strategies for controlling insect vectors of disease. [Review][Erratum appears in Philos Trans R Soc Lond B Biol Sci. 2014 Nov 19;369(1656):20140217]. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences*, *369*(1645). https://doi.org/10.1098/rstb.2013.0432

Burt, A., & Crisanti, A. (2018). Gene Drive: Evolved and Synthetic. *ACS Chemical Biology*, *13*(2), 343–346. https://doi.org/10.1021/acschembio.7b01031

Collins, C. M., Bonds, J. a. S., Quinlan, M. M., & Mumford, J. D. (2019). Effects of the removal or reduction in density of the malaria mosquito, Anopheles gambiae s.l., on interacting predators and competitors in local ecosystems. *Medical and Veterinary Entomology*, *33*(1), 1–15. https://doi.org/10.1111/mve.12327

Connolly, J. B., Mumford, J. D., Fuchs, S., Turner, G., Beech, C., North, A. R., & Burt, A. (2021). Systematic identification of plausible pathways to potential harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector Anopheles gambiae in West Africa. *Malaria Journal*, *20*(1), 170. https://doi.org/10.1186/s12936-021-03674-6

Emerson, C. I., & Singer, P. A. (2010). Is there an ethical obligation to complete polio eradication? *The Lancet*, *375*(9723), 1340–1341. https://doi.org/10.1016/S0140-6736(10)60565-X

Esvelt, K. M., Smidler, A. L., Catteruccia, F., & Church, G. M. (2014). Concerning RNA-guided gene drives for the alteration of wild populations. *ELife*, *3*. https://doi.org/10.7554/eLife.03401

Europäisches Parlament fordert Verbot der Freisetzung von Gene Drive Organismen. (2021, June 9). *STOP GENE DRIVES*. https://www.stop-genedrives.eu/europaeisches-parlament-fordert-verbot-der-freisetzung-von-gene-drive-organismen/

European Commission. Directorate General for the Environment. & University of the West of England (UWE). Science Communication Unit. (2017). *The precautionary principle: Decision making under uncertainty*. Publications Office. https://data.europa.eu/doi/10.2779/709033

Foote, N. (2020, July 3). NGOs call for moratorium on controversial "gene drive organisms." *Www.Euractiv.Com*. https://www.euractiv.com/section/health-consumers/news/ngos-call-for-moratorium-on-controversial-gene-drive-organisms/

Hansson, S. O. (2020). How Extreme Is the Precautionary Principle? *NanoEthics*, *14*(3), 245–257. https://doi.org/10.1007/s11569-020-00373-5

Harremoës, P., & European Environment Agency (Eds.). (2001). *Late lessons from early warnings: The precautionary principle, 1896-2000*. European Environment Agency.

Herren, H., Mooney, P., Suzuki, D., & Ziegler, J. (n.d.). *A Call to Protect Food Systems from Genetic Extinction Technology: The Global Food and Agriculture Movement Says NO to Release of Gene Drives*. ETC Group.

James, S., Collins, F. H., Welkhoff, P. A., Emerson, C., Godfray, H. C. J., Gottlieb, M., Greenwood, B., Lindsay, S. W., Mbogo, C. M., Okumu, F. O., Quemada, H., Savadogo, M., Singh, J. A., Tountas, K. H., & Touré, Y. T. (2018). Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group. *The American Journal of Tropical Medicine and Hygiene*, *98*(6 Suppl), 1–49. https://doi.org/10.4269/ajtmh.18-0083

Kyrou, K., Hammond, A. M., Galizi, R., Kranjc, N., Burt, A., Beaghton, A. K., Nolan, T., & Crisanti, A. (2018). A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. *Nature Biotechnology*, *36*(11), 1062–1066. https://doi.org/10.1038/nbt.4245

National Academies of Sciences, Engineering, and Medicine. (2016). *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK379277/

North, A. R., Burt, A., & Godfray, H. C. J. (2020). Modelling the suppression of a malaria vector using a CRISPR-Cas9 gene drive to reduce female fertility. *BMC Biology*, *18*(1), 98. https://doi.org/10.1186/s12915-020-00834-z

Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13. (2016, December 5). Friends of the Earth International. https://www.foei.org/news/friends-earth-international-160-organizations-called-moratorium-gene-drives-cop-13

Pearson, D. E., Clark, T. J., & Hahn, P. G. (2021). Evaluating unintended consequences of intentional species introductions and eradications for improved conservation management. *Conservation Biology: The Journal of the Society for Conservation Biology*. https://doi.org/10.1111/cobi.13734

Scudellari, M. (2019). Self-destructing mosquitoes and sterilized rodents: The promise of gene drives. *Nature*, *571*, 160. https://doi.org/10.1038/d41586-019-02087-5

Secretariat of the Convention on Biological Diversity (Ed.). (2000). *Cartagena Protocol on Biosafety to the Convention on Biological Diversity: Text and annexes*. Secretariat of the Convention on Biological Diversity.

Stewart Brand. (2010). *Whole Earth Discipline: Why Dense Cities, Nuclear Power, Transgenic Crops, Restored Wildlands, and Geoengineering Are Necessary*. Penguin Books. https://www.biblio.com/book/whole-earth-discipline-why-dense-cities/d/1422510276

Teem, J. L., Ambali, A., Glover, B., Ouedraogo, J., Makinde, D., & Roberts, A. (2019). Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: Results from four regional consultations 2016–2018. *Malaria Journal*, *18*(1), 347. https://doi.org/10.1186/s12936-019-2978-5

Texts adopted—COP15 to the Convention on Biological Diversity (Kunming 2020)—Thursday, 16 January 2020. (2020, January 16). European Parliament. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0015_EN.html

World Commission on the Ethics of Scientific Knowledge and Technology (COMEST). (2005). *The Precautionary Principle* (p. 52). UNESCO. https://unesdoc.unesco.org/ark:/48223/pf0000139578

World Health Organization. (2014). *WHO | The Guidance Framework for testing genetically modified mosquitoes*. WHO. http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/

World Health Organization. (2020a). *World malaria report 2020*. WHO. https://www.who.int/publications-detail-redirect/9789240015791

World Health Organization. (2020b). *WHO Position Statement: Evaluation of genetically modified mosquitoes for the control of vector-borne diseases*. WHO.

World Health Organization. (2021). *Guidance framework for testing genetically modified mosquitoes, second edition* (p. 196) [Guidance Framework]. WHO. https://www.who.int/publications-detail-redirect/9789240025233

Zoloth, L. (2021). The ethical scientist in a time of uncertainty. *Cell*, *184*(6), 1430–1439. https://doi.org/10.1016/j.cell.2021.02.051

Preface to Chapter Three – Articulating ethical principles guiding Target Malaria's engagement strategy

This chapter is constituted by a paper which was published in *Malaria Journal* on February 5, 2022. It has since been accessed over one thousand times. It is a co-authored piece for which I was lead author and contributed conceptualisation, research, analysis, and writing involving original draft preparation and editing. My co-author, Delphine Thizy, was responsible for the methodology and writing involving review and editing. This piece arose out of an invitation to a paper writing collaboration in 2019 from Ms. Thizy, who was at the time Global Stakeholder Engagement Manager for Target Malaria, and in 2020 became Stakeholder Engagement Senior Advisor to Target Malaria, a role she remains in at the time of writing. Target Malaria is a not-for-profit research consortium at the forefront of gene drive science to modify mosquitoes in order to reduce malaria transmission.

Since gene drive is a novel biotechnology, there are currently few best practices available to provide guidance for stakeholder engagement practice. We wrote this paper with the aim of adding to the growing literature regarding stakeholder engagement strategies for gene drive research. This paper aims to articulate the ethical principles guiding Target Malaria's engagement strategy, to explain the rationale for selecting these principles, and share some early lessons about their application. The principles articulated herein provide an ethical structure for decisions relating to Target Malaria's engagement strategy and practices. To date, progress on Target Malaria's scientific research remains in the early stages of its phased approach, with the goal of an environmental release of gene drive modified mosquitoes still years away. In our paper, we outline that different stakeholders must be engaged

proportionally to their ethical relevance to the processes and results of the project. We noted that groups who qualify as the most ethically relevant communities will evolve throughout the project in relation to changing research activities and the scope of their impact.

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COMMENTARY **Open Access**

Articulating ethical principles guiding Target Malaria's engagement strategy

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Abstract

Progress in gene drive research has engendered a lively discussion about community engagement and the ethical standards the work hinges on. While there is broad agreement regarding ethical principles and established best practices for conducting clinical public health research, projects developing area-wide vector control technologies and initiating ambitious engagement strategies raise specific questions: who to engage, when to engage, and how? When responding to these fundamental questions, with few best practices available for guidance, projects need to reflect on and articulate the ethical principles that motivate and justify their approach. Target Malaria is a not-for-profit research consortium that aims to develop and share malaria control and elimination technology. The consortium is currently investigating the potential of a genetic technique called gene drive to control populations of malaria vectoring mosquito species *Anopheles gambiae*. Due to the potentially broad geographical, environmental impact of gene drive technology, Target Malaria has committed to a robust form of tailored engagement with the local communities in Burkina Faso, Mali, and Uganda, where research activities are currently taking place. This paper presents the principles guiding Target Malaria's engagement strategy. Herein the authors (i) articulate the principles; (ii) explain the rationale for selecting them; (iii) share early lessons about the application of the principles. Since gene drive technology is an emerging technology, with few best practices available for guidance, the authors hope by sharing these lessons, to add to the growing literature regarding engagement strategies and practices for area-wide vector control, and more specifically, for gene drive research.

Keywords: Ethics, Stakeholder engagement, Gene drive, Vector control, Malaria, Responsible research, Co-development

Background

In 2021, the World Health Organization (WHO) published the 2nd edition of its guidance for testing genetically modified mosquitoes [1]. A major portion of that report was dedicated to ethical considerations, stressing and the importance of responsible community engagement. Ongoing discussions about genetically modified mosquitoes, including gene drive, tend to focus on ethical aspects of the research [2]. When considering different engagement strategies in the field of gene drive research, it is important to design strategies that are both ethical and effective. At least one other gene drive research programme with malaria elimination goals, the University of California Irvine Malaria Initiative, has published reflections on the formulation of their engagement methodology [3]. By describing their engagement model and its underlying principles, they took an important step towards transparency. This paper aims to do the same by articulating the ethical principles guiding the design and implementation of Target Malaria's engagement strategy.

From the beginning Target Malaria, one of the earliest and most advanced gene drive research projects, initiated a process of formally articulating the project's core values. These values remain in place today:

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- Excellence,
- Co-development,
- Being evidence-driven, and
- Openness and accountability [4]

In further commitments, Target Malaria's engagement strategy has had to align with these values in addition to other ethical principles. For instance, the value of excellence implies aligning with best practices and guidance available in the evolving literature concerning engagement practices for gene drive research.

In what follows, the paper articulates the principles which continue to guide Target Malaria's evolving engagement strategy. The authors also explain the rationale for selecting these principles, which was informed by ethical values, including core project values, emerging guidance and developing best practices in the field. Due to the relative novelty of gene drive technology, the authors aim to contribute to the development of still evolving engagement and best practices in this field.

Case presentation: Target Malaria and gene drive research

Target Malaria is a not-for-profit research consortium that aims to develop and share malaria control and elimination technology. It is currently researching the potential of a biotechnological phenomenon called gene drive to control populations of the mosquito species *Anopheles gambiae*, one of the main vectors of malaria. Gene drive is a term describing the preferential inheritance of a genetic trait in the offspring of a sexually reproducing organism. With the new technique, particular traits can be inherited by close to 100% of the offspring instead of the classical Mendelian inheritance rate, which is approximately 50% [5, 6]. This way, in a sexually reproducing population, traits can spread rapidly, even if the modification does not provide a fitness advantage to individuals who carry it [6]. Gene drive mechanisms are not a novel phenomenon; they occur in nature [5, 7]. In recent years, the original idea of utilizing gene drive to develop a new vector control tool was shown to be possible in the laboratory [8–10]. Given this progress, the Target Malaria strategy to use gene drive to reduce the population of malaria-transmitting mosquitoes below the threshold necessary for effective malaria transmission, interrupting malaria's local transmission in conjunction with other control methods [11], has become a realistic possibility.

Consistent with WHO guidance [1], Target Malaria follows a phased approach, with gene drive mosquitoes representing the ultimate phase: the emergence of a selfsustaining strain able to spread the modification to the target population. The initial phases involve using nongene drive strains of genetically modified mosquitoes [12], which allow for iterative development, integrating learning from previous modified strains to the next phase. This modus operandi also leaves room for piloting the engagement strategy, developed in an early implementation stage according to principles presented here. This is followed by iterative refinement of the engagement strategy along with the changing context of the different research phases.

The nature of gene drive technology poses serious challenges to designing effective community engagement. This is due to the limited availability of past examples of quality engagement practices regarding the application of public health technologies in similar area-wide contexts. Because synthetic gene drives have not been evaluated in the wild and require a methodical stepwise testing pathway [12], communities need to be engaged about overall project goals and methods, as well as the specifics of each research stage. To complicate matters further, each research stage likely involves a different subset within the relevant community. Guidance documents about responsible engagement are still being developed [13, 14]. Target Malaria aims to continue developing its engagement strategy guided by the principles detailed in this article.

The importance of community engagement for a genetic approach to vector control has long been recognized [13–25]. It has been a focal point for Target Malaria since the project's inception, even before its formal establishment as 'Target Malaria'. There are good reasons for designing and enacting a robust engagement strategy around a research project aimed at area-wide vector control. These can be legal, financial, operational, or reputational in nature. However, the authors argue the most important is ethical [25]. This paper articulates Target Malaria's principles for guiding its engagement strategy and explains the rationale for selecting them, grounded in principles and values.

To date, papers and guidelines analysing ethical obligations inherent to engagement practices [1, 18, 23] have primarily focused on the question of consent

to the release of genetically modified mosquitoes [13, 15, 18, 20, 26, 27]. They also suggested that engagement should include a greater degree of partnership than previously seen between researchers and communities living in the research area [3, 14, 18, 23, 24]. When faced with difficult decisions, well-articulated principles can guide a project's strategy design. Still, very little has been written about how and why a given project selects the principles they will follow. This paper explains the rationale behind the four fundamental principles Target Malaria uses to guide its decisions around engagement. These principles are:

1. Prioritize engagement with the most ethically relevant groups
2. Conduct engagement in the spirit and form of codevelopment
3. Engagement activities should be conducted by representatives of the research project
4. Begin engagement early, engage continuously, and iterate often

The paper starts by briefly examining how Target Malaria's project values align with and drive the implementation of a robust programme of principled engagement in the first place.

How Target Malaria's project values motivate commitment to principled engagement

Each of Target Malaria's project values

- Excellence,
- Co-development,
- Being evidence-driven,
- Openness and accountability

are mutually reinforcing, orienting the project towards enacting robust community engagement. For instance, the pursuit of excellence requires for the project to achieve the highest standards of responsible research and best practices. Because a genetic approach to vector control is a fairly new field of research, with yet unestablished best practices, projects engaged in this research have a responsibility to work collaboratively with others to develop them. Excellence and being evidence-driven implies and requires rigorous research, both in the laboratory and in the communities and ecosystems where the research is conducted, to benefit the people the research aims to help. In Target Malaria's case, it is these same communities that bear most of the risk of the research.

From the start, Target Malaria has been committed to the values of co-development, openness, and accountability. The project prioritized these values because they are underwritten by a core tenet of ethical research: respect for persons [28]. Engaging affected parties openly and accountably with the aim of being granted consent—or in the case of a community-wide intervention like gene drive, community agreement [29]—reflects this respect for persons. This normative process is a prerequisite for any research activity that potentially impacts human beings. For this reason, the project's values compel it to engage in this manner whether or not external requirements or regulations demand it. This is important since external requirements for engagement for gene drive research are in many cases still under development.

Commitment to the values of openness and accountability require that Target Malaria engages transparently with communities, stakeholders, and the public about its work. Being accountable implies a further commitment to the value of justice, both substantively and procedurally. This demands that the project avoid and/or manage a potential adverse impact on communities and the environment where they live. It also explores how benefits for communities and other stakeholders can be maximized by investing in local capacity building. The project should also give relevant communities the opportunity to voice their concerns and share with the project first-hand knowledge of their own needs and values and insight into their interaction with and dependence on the local environment. Doing so can help inform the project of a broader scope of relevant risks and related protection goals than could have been identified otherwise, further minimizing potential harm [24].

The value of co-development requires that communities are empowered with an informed and impactful voice in decisions that will affect them and the design of the processes by which those decisions are made. Because openness and accountability are analogues for honesty and trust [4], the engagement strategy needs to foster and build trust. The only way to do this is through numerous interactions over an extended period and consistent demonstration of honesty, reliability, accountability, and good-faith behaviour.

Although the above does not provide an exhaustive analysis, Target Malaria's decision to make its project

values explicit provides the ethical mandate for answering further questions regarding designing an ethical engagement strategy. These values subsequently informed the selection and articulation of principles to guide the design of an engagement strategy for Target Malaria's gene drive research project. The remainder of this Commentary explains in greater detail the rationale behind the selection of each of Target Malaria's engagement principles.

For examples of how these principles (Fig. 1) inform Target Malaria's community engagement protocols and

Fig. 1 Guiding Principles for Ethical Engagement

practices, please see "Small-scale release of non-gene drive mosquitoes in Burkina Faso: from engagement implementation to assessment, a learning journey" by Lea Pare Toe et al. [30].

Prioritize engagement with the most ethically relevant groups

In reference to its recommendations around engagement practices, the 2016 report *Gene Drives on the Horizon*, published by the National Academies of Sciences, Engineering, and Medicine (henceforth, the NASEM Report), distinguishes between communities, stakeholders, and publics [23]. Each of these groups has some stake in the outcome of a gene drive project, and as such, all deserve to be engaged about the project in a manner appropriate to their context and needs. Nevertheless, the consequences of the research, whether harm or benefit, resulting from a decision to proceed with the research or not, will be borne to differing degrees by each of these groups. They will be borne most directly and heavily by the relevant communities. To engage each group, communities, stakeholders, and public in the same way or with the same prioritisation of time, resources, consideration, and importance would be inappropriate. Instead, in alignment with the project values of accountability and basing decisions on evidence, each group should be engaged with priorities proportional to their ethical relevance to the processes and results of the project. The degree of ethical relevance of a group is to be assessed via a formal impact analysis; how likely and significantly will they be affected as a consequence of the project's activities, whether positively or negatively.

Of the three groups, communities, as defined by the NASEM report definition, have the greatest and most direct stake in the processes and outcomes of project activities. This greater stake grants them greater ethical relevance. Identification of a community's ethical relevance necessitates a systematic review of how the project (both with the mosquito strain itself and proposed activities such as monitoring) will potentially impact the community socially, economically with regards to public health and their access to and use of ecosystem services [31]. It is only reasonable that more significant consideration should be offered to those most likely to be directly and consequentially impacted by the research process and results. This greater consideration should be demonstrated by prioritising and empowering the communities identified as most relevant to have meaningful input— throughout the project cycle— regarding the research project's goals and the design of its processes [14, 32, 33].

The set of communities identifiable as the most ethically relevant will evolve throughout the project in relation to the proposed activities and the mosquito strain used (based on their potential dispersal and persistence), and the type of entomological activities. For example, the potential impact on communities' daily lives is different if the project collects mosquitoes using an insecticide spray and catch technique (which requires entering people's homes) versus using the swarming capture technique (which takes place outside in the village common area) [34]. Several studies inform the project's identification and analysis of community relevance, some directly carried out by the project (such as modelling studies), others by external experts or via considerations found in the growing engagement literature. Ultimately, the identification of ethically relevant communities is reviewed by the institutional ethics committee that, in the end, must approve the scope of the engagement

work, including from whom consent and/or community agreement will have to be obtained.

The conviction that the most ethically relevant communities ought to be engaged more robustly and be directly involved in the project's deliberative processes arise out of the project's commitment to accountability, a value underwritten by the more fundamental values of respect for persons and justice; both substantive and procedural. Substantive justice entails the sense that there should be an appropriate balancing of the cost and benefits ultimately realised through the research project. Procedural justice prescribes that those who will be subject to the research outcomes are empowered to exert significant influence on the project design and implementation through co-development mechanisms.

Target Malaria's engagement strategy embodies its commitment to the principle of prioritising the most ethically relevant groups, demonstrated for instance by its generous allotment of time and resources to engagement. The role of Target Malaria's international-level engagement with stakeholders and the public has been filled by a single person for a long time. In contrast, around 20 individuals employed by the project are engaging communities in the three African partner countries. An approach focused on political expedience might have committed more resources to the international and panAfrican political and regulatory levels, which enjoy more media attention and where more influence can be exerted to expedite the progress of the research. Instead, the project decided to devote greater engagement resources to those groups that are most ethically relevant; the communities which the research is more likely to affect.

Applying this principle has not been without challenges. The communities that face the highest malaria burdens are often rural, sometimes isolated, and in many cases have limited access to formal education and public health facilities. These circumstances pose additional challenges to ensuring that the most relevant communities are equipped and feel empowered to make informed decisions. Most commonly, deliberations related to research and innovation in the field of public health do not include these communities. Others who might have more social or political capital tend to influence those decisions. However, limited access to education and overall social and economic disenfranchisement should not constitute grounds for being excluded from deliberation. The values of accountability, respect for persons, and justice continue to motivate Target Malaria to ensure that affected communities can understand and decide for themselves if, how, and when the project should proceed.

Conduct engagement in the spirit and form of co-development

Co-development can be defined as "a collaborative process of jointly designing a research pathway and its resultant intervention to reach a common goal" [25]. What makes the relationship between a research project such as Target Malaria's and the communities in which it would operate an ethical imperative? For starters, genuine co-development promotes and results in capacity building in and empowerment of the involved communities.

The NASEM report states:

The ability of people in low-income countries to participate meaningfully in decision making would be supported best not by merely engaging them in decisionmaking, but by building the capacity in those countries to conduct locally valuable research, regulate and provide oversight of gene drive research generally, and carry out their own decision making about its application. To ensure that capacity-building activities are not just a guise for off-loading expensive and risky research—perpetuating rather than addressing injustice—such activities need to include the development not just of technical capacity to do research but also of capacity to oversee safe and responsible research practices and decide how best to use research findings. Genuine capacity-building must be understood as empowerment, and empowerment must mean that a community or country is able to act on its values rather than merely relying on values imported from elsewhere [23].

This passage aptly describes a significant part of why co-development is both useful and essential. Co-development mitigates against the dynamic of researchers controlling the process and outcome of a project, which is especially important when it involves researchers from high-income countries (HICs) operating in low- and middle-income countries (LMICs). Particularly in relationships involving this kind of power imbalance, building and maintaining the more vulnerable party's trust is important for the ethical legitimacy of the ongoing partnership. Target Malaria's partnerships with local communities in Burkina Faso, Mali, and Uganda reflect this concern.

For example, when the project started considering how to achieve meaningful community-level

acceptance for some of its activities (initially for mosquito collecting activities in swarms, which occur in the community space), the project chose to co-develop the acceptance model with the community (Fig. 2).

Co-development integrates constraints from both sides. For instance, the research project's need to record the result of the deliberation was accommodated by the community. This process resulted in a model that satisfied both the community and the researchers. It was subsequently approved by an institutional ethics committee, ensuring that the process was co-developed and in line with established obligations of ethical research to protect participant communities. In the project's guidance documents, engagement with a qualified and appropriate ethics committee is specified as an essential part of a responsible co-development model [13, 14].

In the case of Target Malaria, various ethics committees are involved. At the African partner level, the institutional ethics committee has oversight of overall project activities, which includes reviewing fieldwork protocols as well as engagement protocols, but also ensuring that these protocols are implemented. For example, in the case of the recent release of non-gene drive sterile male mosquitoes in Burkina Faso, the institutional ethics committee observed the release process, thereby providing formal ethical oversight.

In addition, the project has set-up an Ethics Advisory Committee [30, 35] to provide recommendations on the non-scientific aspects of the research. These include stakeholder engagement activities and a community acceptance model. This committee does not exercise oversight but provides a forum through which the project receives input and criticism about its approach. Its overall objective is learning and improvement.

Co-development looks different from case to case. Ethically designed engagement does not result from a predictable, uniform process. It must be designed on a case-by-case basis and tailored to the communities and research projects which participate in the co-developed engagement process. An ethical engagement process must be a bilateral process. This contrasts with a oneway download of information from the project to the community. The traditional knowledge-deficit engagement model tends towards top-down activities designed to educate the public about the benefits of the technology to secure acceptance or consent for a field evaluation [24]. A co-development relationship should be viewed as essential not only to decision-making processes and a final decision as to *whether* the research will proceed (substantive justice), but also *how* the research should proceed (procedural justice).

For example, deliberative processes vary from culture to culture. What's ethically mandated in the USA or Europe may not meet local ethical norms in rural Burkina Faso. A given community may not

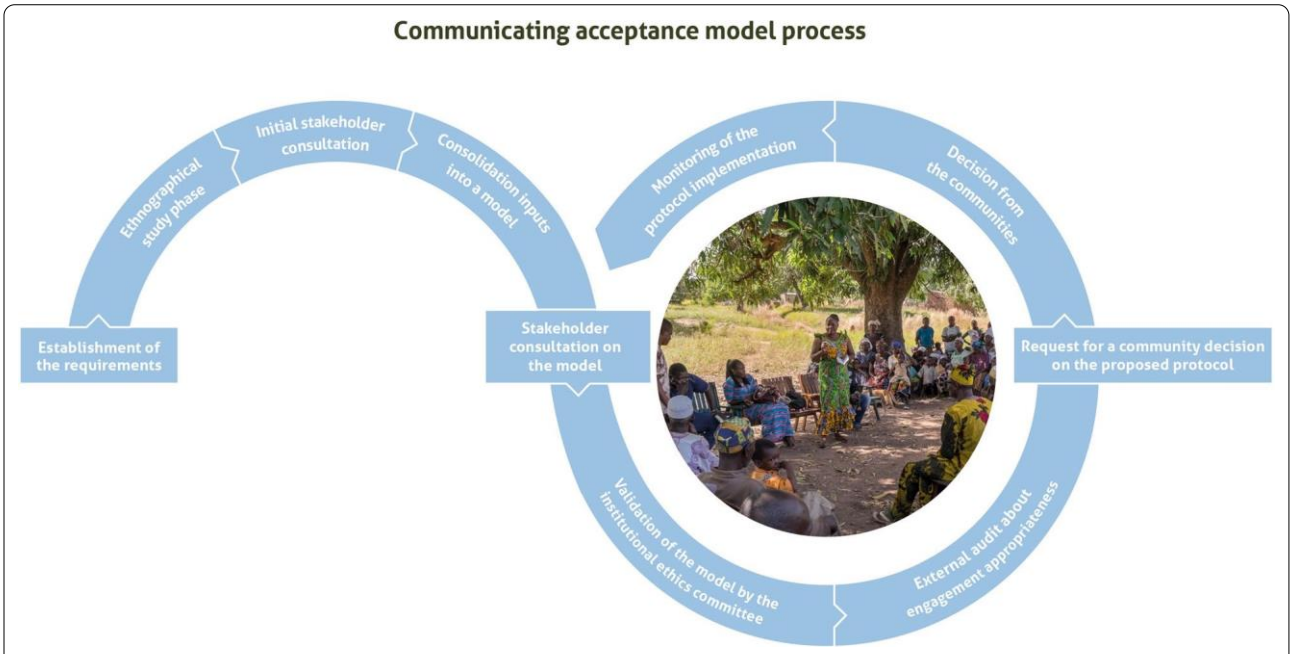

Fig. 2 Target Malaria's co-development process for community agreement

employ democratic methods of deliberation. For various reasons, the methods they rely on may not bestow the same level of voice or agency on all the minority groups that are part of that community. Accepting the results of such deliberative structures may be called into question by an ethics committee or project critics. However, there is no onesize-fits-all ethical discourse on how best to deliberate as a community [36]. Ultimately, to be legitimate, the design of deliberative processes should be sensitive to the context they are designed for [18, 37].

Engaging in co-development can aid the comprehension of processes that are different from one's own and can serve to bridge practical divides. This, in turn, facilitates a give-and-take process that can accommodate all involved parties by honouring procedural justice in the design of deliberation processes [38]. This way, the process of ethical engagement, honouring the principle of respect for persons, closely mirrors the process of seeking informed consent. It is inappropriate for project researchers or the engagement team to impose deliberative structures on the communities they engage with. It would be inappropriate for a physician conducting clinical research to impose their beliefs about how to deliberate on a clinical research participant. Unless significant internal conflict exists about the deliberative structures in place within the community, challenging these structures from an outsider's position can be seen as disrespectful, potentially creating harmful conflict.

Essentially, co-development is the process by which parties working together towards a common goal practice their partnership through continual open conversation and mutual iteration. Through this process, several essential things may be achieved: the design of mutually agreed upon project processes, increased receptivity and trust on both sides of the partnership, capacity building and empowerment of initially disempowered and vulnerable communities, and ultimately the best research product possible with the least harm or injustice incurred along the way toward achieving it. A positive side effect of co-development done well is that the trust and goodwill fostered between the parties involved can also provide a foundation for enduring friendship and future partnerships.

Engagement activities should be conducted by representatives of the research project

From Target Malaria's conclusion that co-development is the most ethical form of engagement for this project, follows that it is internal representatives of the research consortium that should conduct the engagement activities, fulfilling their part of the partnership role as laid out in the section above. As recommended in existing guidance literature, employing a multidisciplinary team which integrates stakeholder engagement, communication, and community mobilization experts is critical [1, 14, 25]. Target Malaria's engagement work is led by social scientists and engagement practitioners from the countries where the engagement occurs. However, other project scientists also play an important role in engagement. They are frequently trained on how to share their knowledge and listen to stakeholder knowledge in a culturally relevant way [39]. In contrast, some authors have suggested that in order to avoid conflicts of interest, engagement for gene drive research projects should be carried out through 'neutral' third party bodies responsible for convening, facilitating, and recording the outcomes, for instance, during a forum for communities, technology developers, and governments [40]. Convening such a large and disparate group raises serious questions about feasibility. For instance, how to fund the work of such a body, or how to ensure it is and remains neutral? However, such questions will not be explored here. Instead, the paper will look at Target Malaria's reasons for preferring direct engagement of relevant communities by project representatives.

Target Malaria believes that a project should be codeveloped in close partnership with the communities in which it operates and affected by the project's research activities. Engagement characterized by co-development requires the building of relationships and fostering of trust between the research consortium and the relevant communities, facilitated by direct engagement and partnership activities. Once this trust is earned and maintained, a free flow of information between the partners can begin. Adding what amounts to a 'middleman' to the equation muddles this relationship, adding unnecessary bureaucracy and lengthening communication lines, increasing the opportunity for miscommunication. It also creates a nexus of significant political power in the decision-making process that could be susceptible to influence.

Insisting on the creation of a 'neutral' third party engagement facilitator may sow the seeds of mistrust since the belief that one is required implies that, without such a body, the would-be partners are likely to act in bad faith or are otherwise incapable of interacting together constructively without third party facilitation.

Target Malaria's co-development model is not naïve to potential conflicts of interest, featuring safeguards to mitigate against them. Some of these safeguards come in the form of the ethical principles the project has developed, which include the project's stated values, the guiding principles mentioned here, in addition to abiding by the required review and approval by an ethics committee each time before proceeding with iterative process changes. The ethics committee provides confidence in the ethical legitimacy of project processes through oversight without getting in the middle of the partnership and complicating communication. As an aside, co-development requires and facilitates engagement of the knowledge of the relevant communities to inform the product and processes of the project. This would be made much more difficult, perhaps impossible if it had to be done through a third-party body. However, specific activities (like evaluations) may require third-party intervention, and likewise, other stakeholders might want to initiate engagement of their own with the communities and/or the researchers.

Begin engagement early, engage continuously, and iterate often

This principle echoes recommendations found in several articles and guidance documents which address the subject of community engagement for genetically modified mosquito research projects [14, 22, 41, 42]. Target Malaria's commitment to excellence requires alignment with consensus best practices in the field. "Engaging early and often with regulators" and ensuring that "stakeholders will be engaged at all stages of trials preparation" are some of the core commitments made by researchers for field trials of gene drive organisms [43]. But how early is early enough, or conversely, too early to engage? These questions are often raised in discussions around gene drive, considering that for many projects, funding for engagement is not necessarily available before they have a proof of concept in the laboratory. The challenges of funding and risks associated with early engagement, many years before field evaluation is even envisaged, can deter many researchers. As a result, very often, "engage early" is taken to mean "engage early in the stages *after* you have a working construct and are preparing for a field evaluation".

When in the project's life cycle should relevant communities be engaged? Co-development requires engagement with the community at a very early stage to avoid the perception that co-development only began once most of the decisions had already been taken. The project's stepwise approach decided upon in order to empower African researchers, building knowledge through iterative constructs, and building trust and confidence with stakeholders required that Target Malaria's engagement activities started (in 2014) years before the proof-ofconcept gene drive construct was achieved in the lab (in 2019).

Adhering to this principle includes working with vulnerable populations that are the most ethically relevant to the project. This requires a step-by-step engagement process to build the community's understanding of the basic concepts and nature of the science employed by the project so they can make legitimately informed decisions about it [44]. Providing this information required first analysing the communities' existing level of technical knowledge with regards to the proposed genetic approach, including malaria transmission mechanisms, genes, genetic inheritance. This happened before specific information about the mosquito strains that are part of Target Malaria's evaluation pathway was introduced. The process required, as a first step, working towards a mutual understanding with the community about vocabulary and concepts, such as *gene*, *genetic trait*, *genetic inheritance*, and conducting subsequent testing to ensure a mutual understanding of these concepts to a degree that enabled joint decision-making. This was done by codeveloping a glossary in local dialects shared by researchers and the community.

As stated above, engagement should facilitate and be characterised by co-development, tailored to and prioritising the most ethically relevant communities. This is a complex and time-consuming process, which must take place in parallel with each successive stage of the project's design and development. Only this way can relevant local community input be effectively harnessed at the earliest designing stage. The engagement processes themselves should also be designed together. For reasons of procedural justice described earlier, this too should happen at the earliest stages of the project's conception. At a minimum, engagement with relevant communities should occur

before bringing any non-engagement-related project activities into the geography of the relevant community [14].

The most fundamental goals of the project should be shaped in partnership with relevant communities prior to the building of significant momentum in any direction. In other words, engagement should begin during the early planning stages of a project's transition from the discovery phase to a development/evaluation phase. This engagement process should pervade all aspects of the project at each stage and inform the fundamental shape and goals of the project itself.

As regards Target Malaria's work in Burkina Faso, Mali and Uganda, communities identified as the most ethically relevant, receiving the most robust engagement, are broadly speaking underprivileged communities with low rates of access to education. Although they have been identified as the most relevant, conducting appropriately thorough, ethically sound engagement with these communities is a resource-intensive process that presents many challenges. Traditionally, engagement has not received adequate budgets. By contrast, between 2016 and 2020, Target Malaria's engagement budget for Burkina Faso represented approximately 23% of the total project budget for that country, as required by the project's ethical commitments. Reaching this level of funding for engagement activities and for identifying needs and objectives to be fulfilled by subsequent engagement designs was only possible because early-stage fact-finding engagement activities had already been funded and conducted. In short, when it comes to engagement, it's important to start early. The ethical imperative of making sure this kind of engagement can take place falls mainly on the shoulders of the research funders [45].

A project's ability to engage continuously and iterate often based on outcomes and understandings gained through earlier engagement is contingent on starting early but also on maintaining regular engagement activities. This means that mechanisms should be in place to facilitate regular bi-lateral communication between project personnel and partner communities. This includes complaint response mechanisms. Doing so is of vital ethical importance, as it is through such processes that communities are informed about the project. In turn, the project could become informed and influenced by empowered voices emanating from the community. Only through continuous bi-lateral communication can both partners be updated on the other's needs and opinions to be integrated in decisions made throughout the project life cycle.

In addition to consistent, regular engagement, it is vital that the project be endowed with mechanisms to ensure knowledge engagement [24, 43] and that community opinions discovered through those engagements are iteratively integrated back into the project design and processes. Examples of potential mechanisms for this have been tested by Target Malaria as described by Pare Toe et al. [30] regarding their work in Burkina Faso. If a project fails to develop and enact mechanisms to facilitate this iteration, then for all the information the engagement might produce, they are not effectively performing their role of ensuring a community voice in, and therefore co-development of, the project. It is the authors' belief that a project which fails in this way also fails in its ethical obligations to respect the people in the communities where the research is conducted. It would represent a failure of procedural justice; a failure to empower and regularly update but also be updated by the communities, crucially denying them a say in how or whether the research project should proceed. Procedural justice and accountability also mean starting engagement early, engaging continuously, and iterating often. It also contributes to substantive justice by avoiding or minimizing harm as well as achieving the greatest possible benefit to communities.

Conclusion

This paper has aimed to articulate the principles guiding Target Malaria's engagement strategy, to explain the rationale for selecting these principles, and share some early lessons about their application. Since gene drive technology is an emerging technology with yet to be established best practices in the field, the authors hope by sharing these early lessons to add to the growing literature regarding engagement strategies and practices for area-wide vector control, and more specifically, gene drive research. The principles Target Malaria selected to guide its engagement strategy are:

1. Prioritise engagement with the most ethically relevant groups.
2. Conduct engagement with these groups in the spirit and form of co-development.
3. Engagement should be conducted by representatives of the research project.

4. Begin engagement early, engage continuously, and iterate often.

These principles continue to inform and provide an ethical structure for decisions relating to Target Malaria's engagement strategy and practices.

To date, progress on Target Malaria's testing pathway remains in the early stages of its phased approach, with the goal of environmental release of gene drive modified mosquitoes still years away. Future phases represent novel and hitherto unresolved challenges to designing an ethical engagement strategy. One of these challenges is to appropriately identify, define, and delineate the ethically relevant communities that should be engaged in advance of a mosquito release involving gene drive modification. To address these, a dialogue is required during and after the impact assessment process to ensure a common understanding among stakeholders about who the impacted communities are and their prioritisation in the engagement process. Existing impact assessment best practices put that engagement at the heart of the process [46].

As the geographic area and number of people whose environment will be directly affected by the project expands, the project will face an additional challenge. How can tensions between ensuring culturally appropriate representation in decision-making models and inclusive representation of marginalised groups best be addressed or managed? And what role should external auditors/certifiers play in project activities related to the community acceptance-seeking process and post-release monitoring?

In 2020 the project initiated a consultation process with stakeholder engagement experts, bioethicists, and socio-anthropologists—mainly from Africa—to start an initial conceptualisation of these issues. The principles described here and the values that inform them will be instrumental to devising solutions to these challenging questions. The authors hope that sharing these ethical foundations supporting Target Malaria's engagement strategy will inspire broad reflections about the design of frameworks for ethics-based case-by-case engagement strategies, particularly for area-wide and public health research and applications.

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Authors' contributions

AJR: Conceptualisation, Research, Analysis, Writing – Original Draft Preparation & Editing. DT: Methodology, Writing – Review & Editing. Both authors read and approved the final manuscript

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Availability of data and materials

No data or materials are associated with this article.

Declarations

Ethics approval and consent to participate

The work described in this paper was carried-out mainly between 2014 and 2020 and was covered by the following ethics approvals:
From the Comité d'Éthique Institutionnel du Centre Muraz, Burkina Faso (Institutional Ethics Committee of the Muraz Centre): 009–2012/CE/CM;
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CE/FMPOS and 2019/ 118 /CE/FMPOS;
From the Ugandan Virus Research Institute Research and Ethics Committee:
UVRI-GC/127/14/02/348, UVRI-GC/127/18/01/600, UVRI-GC/127/16/11/348,
UVRI-GC/127/21/01/807;
From the Ugandan National Council for Science and Technology: UNCSTHS1328-2015, UNCST-HS1328-2016, UNCST-HS2378-2018.

Consent for publication

There is no individual data in this paper requiring prior consent before publication.

Competing interests

The authors have no interest to declare.

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References

1. WHO. Guidance framework for testing genetically modified mosquitoes, Second edition, Geneva, World Health Organization, 2021. Available from: https:// www. who. int/ publi catio ns/i/ item/ 97892 40025 233
2. de Graeff N, Jongsma KR, Bredenoord AL. Experts' moral views on gene drive technologies: a qualitative interview study. BMC Med Ethics. 2021;22:25.
3. Kormos A, Lanzaro GC, Bier E, Dimopoulos G, Marshall JM, Pinto J, et al. Application of the relationship-based model to engagement for field trials of genetically engineered malaria vectors. Am J Trop Med Hyg. 2021;104:805–11.
4. Target Malaria. Mission Vision Value Statement. 2017. Available from: https:// targe tmala ria. org/ wp- conte nt/ uploa ds/p df/ missi on- vision- values- state ment. pdf
5. Burt A, Trivers R. Genes in conflict: the biology of selfish genetic elements. Harvard University Press, 2007.
6. Burt A, Crisanti A. Gene drive: evolved and synthetic. ACS Chem Biol. 2018;13:343–6.
7. Wedell N, Price TAR, Lindholm AK. Gene drive: progress and prospects. Proc Biol Sci. 2019;286:20192709.
8. Burt A. Site-specific selfish genes as tools for the control and genetic engineering of natural populations. Proc Biol Sci. 2003;270:921–8.
9. Simoni A, Hammond AM, Beaghton AK, Galizi R, Taxiarchi C, Kyrou K, et al. A male-biased sex-distorter gene drive for the human malaria vector *Anopheles gambiae*. Nat Biotechnol. 2020;38:1054–60.
10. Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, et al. A CRISPR-Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. Nat Biotechnol. 2018;36:1062–6.
11. Eckhoff PA, Wenger EA, Godfray HCJ, Burt A. Impact of mosquito gene drive on malaria elimination in a computational model with explicit spatial and temporal dynamics. Proc Natl Acad Sci USA. 2017;114:E255–64.
12. Windbichler N, Papathanos PA, Crisanti A. Targeting the X chromosome during spermatogenesis induces Y chromosome transmission ratio distortion and early dominant embryo lethality in *Anopheles gambiae*. PLoS Genet. 2008;4:e1000291.
13. WHO. Guidance, ethics and vector borne diseases [Internet]. Geneva, World Health Organization, 2020. Available from: https:// apps. who. int/ iris/ bitst ream/ handle/ 10665/ 336075/ 97892 40012 738- eng. pdf
14. James S, Collins FH, Welkhoff PA, Emerson C, Godfray HCJ, Gottlieb M, et al. Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in Sub-Saharan Africa: recommendations of a scientific working group†. Am J Trop Med Hyg. 2018;98:1–49.
15. Resnik DB. Ethical issues in field trials of genetically modified diseaseresistant mosquitoes. Dev World Bioeth. 2014;14:37–46.
16. Kaebnick GE, Heitman E, Collins JP, Delborne JA, Landis WG, Sawyer K, et al. Precaution and governance of emerging technologies. Science. 2016;354:710–1.
17. African Union. Gene drives for malaria control and elimination in Africa. 2018.
18. WHO/TDR and FNIH. Guidance Framework for testing genetically modified mosquitoes. Geneva: World Health Organization; 2014.
19. WHO. Progress and prospects for the use of genetically modified mosquitoes to inhibit disease transmission. Geneva, World Health Organization, 2009.
20. Kolopack PA, Lavery JV. Informed consent in field trials of gene-drive mosquitoes. Gates Open Res. 2017;1:14.
21. Kolopack PA, Parsons JA, Lavery J V. What makes community engagement effective?: lessons from the Eliminate Dengue program in Queensland Australia. PLoS Negl Trop Dis. 2015;9:e0003713.
22. Resnik DB. Ethics of community engagement in field trials of genetically modified mosquitoes. Dev World Bioeth. 2017;375:135–43.
23. Committee on Gene Drive Resarch in non-human organisms. Gene drives on the horizon:advancing science, navigating uncertainty, and aligning research with public values.Washington, National Academies of Sciences Engineering and Medicine. 2016. https:// doi. org/ 10. 17226/ 23405. Available from: http:// www. nap. edu/ catal og/ 23405
24. Hartley S, Thizy D, Ledingham K, Coulibaly M, Diabaté A, Dicko B, et al. Knowledge engagement in gene drive research for malaria control. PLoS Negl Trop Dis. 2019;13:e0007233.
25. Thizy D, Emerson C, Gibbs J, Hartley S, Kapiriri L, Lavery J, et al. Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods. PLoS Negl Trop Dis. 2019;13:e0007286.
26. Neuhaus CP, Caplan AL. Ethical lessons from a tale of two genetically modified insects. Nat Biotechnol. 2017;35:713–6.
27. Singh JA. Informed consent and community engagement in open field research: lessons for gene drive science. BMC Med Ethics. 2019;20:1–12.
28. Lysaught MT. Respect: or, how respect for persons became respect for autonomy. J Med Philos. 2004;29:665–80.
29. Thizy D, Pare Toe L, Mbogo C, Matoke-Muhia D, Alibu VP, Barnhill-Dilling SK, et al. Proceedings of an expert workshop on community agreement for gene drive research in Africa - Co-organised by KEMRI, PAMCA and Target Malaria. Gates Open Res. 2021;5:19.
30. Pare Toe L, Nourou B, Ky AD, Kekele S, Wilfrid M, Bayala K, et al. Smallscale release of non - gene drive mosquitoes in Burkina Faso: from engagement implementation to assessment, a learning journey. Malar J. 2021;20:395.
31. IAIA. What Is Impact Assessment? 2009.
32. George DR, Kuiken T, Delborne JA. Articulating "free, prior and informed consent" (FPIC) for engineered gene drives. Proc Biol Sci. 2019;286:20191484.
33. Council for International Organizations of Medical Sciences, and WHO. International ethical guidelines for health-related research involving humans. Geneva, World Health Organization, 2016. Available from: https:// cioms. ch/ publi catio ns/ produ ct/ inter natio nal- ethic al- guide lines- for- health- relat ed- resea rch- invol ving- humans/
34. Birungi K, Mabuka DP, Balyesima V, Namukwaya A, Chemoges EW, Kiwuwa-Muyingo S, et al. Eave and swarm collections prove effective for biased captures of male *Anopheles gambiae* mosquitoes in Uganda. Parasit Vectors. 2021;14:281.
35. Target Malaria. Ethics Advisory Committee. 2021 [cited 2021 Sep 29]. Available from: https:// targe tmala ria. org/ about-us/ ethics- advis ory- commi ttee/
36. Christakis NA. Ethics are local: engaging cross-cultural variation in the ethics for clinical research. Soc Sci Med. 1992;35:1079–91.

37. O'Doherty KC. Deliberative public opinion: development of a social construct. Hist Human Sci. 2017;30:124–45.
38. Miller D. Justice. Stanford Encycl Philos. 2017
39. Wanyama Chemonges E, Pare Toe L, Dicko B, Coulibaly M. Co-developing a common glossary with stakeholders for engagement on new genetic approaches for malaria control in a local African setting. Malar J. 2021;20:53.
40. Kofler N, Collins JP, Kuzma J, Marris E, Esvelt K, Nelson MP, et al. Editing nature: local roots of global governance. Science. 2018;362:527–9.
41. Rortais A, Arnold G, Dorne J Lou, More SJ, Sperandio G, Streissl F, et al. Risk assessment of pesticides and other stressors in bees: principles, data gaps and perspectives from the European Food Safety Authority. Sci Total Environ. 2017;587–8:524–37.
42. Lavery JV, Tinadana PO, Scott TW, Harrington LC, Ramsey JM, YtuarteNuñez C, et al. Towards a framework for community engagement in global health research. Trends Parasitol. 2010;26:279–83.
43. Long KC, Alphey L, Annas GJ, Bloss CS, Campbell KJ, Champer J, et al. Core commitments for field trials of gene drive organisms. Science. 2020;370:1417–9. Available from: http://science.sciencemag.org/content/370/ 6523/1417.abstract
44. Swetlitz I. Gene drives could halt malaria in West Africa — if residents agree to it. STAT News. 2017.
45. Emerson C, James S, Littler K, Randazzo F. Principles for gene drive research. Science. 2017;358:1135–6.
46. Enserink B, Connor D, Croal P. Public participation: international best practice principles. Spec Publ Ser. 2006;34:3.

Publisher's Note

Preface to Chapter Four – Identifying a normatively legitimate political locus of deliberative authority for environmental release of gene drive modified organisms

The papers forming the first two chapters of this thesis analysed and offered rebuttals to critiques of gene drive technology which claim it would be unethical to develop and/or use it in an open environment. In chapter three principles informing Target Malaria's engagement strategy were articulated and their analytical rationale provided for their selection. It would be fair to say that a thematic thread running through this thesis relates to questions of deliberation about whether, when, and in what context it is appropriate to use gene drive technology, particularly in mosquitoes for malaria elimination. This fourth and final chapter is constituted by an article which carries that thematic thread forward by posing, and offering a considered answer to, the question: Who has justified authority to decide whether to release gene drive modified organisms? Put another way; from whom, or what political level of organization, should developers of gene drive technology seek final authorization for environmental introduction of gene drive organisms? Given the inherent and necessarily non-individualized effects of gene drive technology, individual consent will not do for legitimization of its environmental release. It becomes clear this is a question about identifying the appropriate political locus of deliberation. This paper explores available levels of political organization, or jurisdiction, in relation to the features characteristic of gene drive technology; the capacities of each, and scopes of legitimate authority of each, in a general manner, in order to offer some initial broad-strokes guidance regarding where it would be appropriate to seek such authorization from.

Chapter Four – Identifying a normatively legitimate political locus of deliberative authority for environmental release of gene drive modified organisms

1. Introduction

This paper offers an analysis which aims to identify the level of political organization at which it is ethically most appropriate to seek consent or authorization to deploy gene drive modified mosquitoes for the purpose of malaria elimination. It will not examine in any depth appropriate deliberative processes, only the appropriate primary political locus of deliberative gravity – in other words, the most legitimate authority to make a gene drive release decision. It takes as a starting point for analysis our present place in geo-political history, and only existing political, technical, and regulatory structures and institutions. I will add also, because conceptions of political legitimacy can vary quite a bit, that I take a take a rational proceduralist view of democratic legitimacy which adds conditions which refer to the quality of outcomes to those that apply to the procedural aspects of democratic deliberation (Peter, 2017). Which is to say, while some degree of procedural justice is necessary, I do not take it as sufficient for achievement of legitimacy. Also necessary are beneficial outcomes which fulfil requirements of substantive justice.

I will first make clear why both individual informed consent as well as community-level consent fail to provide ethical justification for authorization for an open release of gene drive modified mosquitos. Following that, I will explain why a primarily global, or inter-governmental, level of deliberative authority also fails to provide normative legitimacy as a primary locus of such decision making. I will defend the view that in our current geo-political context it is most ethically appropriate to seek political authorization for release of gene drive applications into the environment from the governing and or regulatory institutions of a nation-state. I do so on the grounds that, generally, nation-states provide the best existing platforms for

legitimate authoritative decision making – i.e. appropriately balancing considerations of consent, beneficial consequences, public reason, and democratic approval – around a technology with the attributes of engineered gene drive. Lastly, I will qualify my stance by identifying some aspects of gene drive governance most ideally handled at the international (though not necessarily global) level, such as providing fora for sharing guidance and regulatory best practices, and for regional international cooperation and consensus building around these issues.

2. Overview

Naturally evolved gene drive, or "selfish" genetic mechanisms have long been observed in nature (Alphey et al., 2020; Burt & Crisanti, 2018). These have inspired the vision and scientific work towards engineering purpose-built gene drive molecular mechanisms to aid efforts towards pest elimination for decades (Burt, 2003; Gould & Schliekelman, 2004). For a long time, progress on this work was very slow and remained in very early stages of research due to available methods of genetic engineering. However, it was discovered as recently as 2014 that utilization of the CRISPR-Cas9 gene editing mechanism (a gene editing tool discovered only in 2012) enables faster, more precise, and cost-effective development of engineered gene drive biotechnology (Esvelt et al., 2014; Kyrou et al., 2018; Simoni et al., 2020). Almost overnight the prospect of developing engineered gene drive mosquitoes as a tool for furthering malaria elimination efforts became a technically viable and promising option for innovating the malaria elimination tool kit.

At the time of writing, there have been no published environmental releases of organisms carrying a gene drive. We can contain the spread of gene drive organisms within laboratory conditions with physical barriers and containment protocols. As many stages of step-by-step

testing as possible are being conducted in successively larger and more sophisticated contained laboratory environments in order to replicate more closely natural ecological conditions and thereby safely test for efficacy (Hammond et al., 2021). This practice aligns with several sources of guidance that recommend the testing pathway prior to open release be cautious and step-wise (Annas et al., 2021; James et al., 2018; Long et al., 2020; National Academies of Sciences, Engineering, and Medicine, 2016; World Health Organization, 2021). However, once all possible and useful testing in the laboratory is complete and yielding satisfactory results, it will be necessary to test the real-world viability of gene drive organisms in an uncontained environment amidst wild-types of their species because experimental results in laboratory conditions and within lab raised organisms cannot be depended upon to be perfectly representative of performance in the wild (Beans, 2018; Dutra et al., 2015; Oliveira et al., 2017); the context for which these technologies are being developed. The catch is that field testing gene drive mosquitoes in the environment, if the drive is stable and successful, could amount to a de-facto deployment of the technology; deployment of a not-yet-fully-tested technology. Further, there is currently no proven method for recall or halting the self-sustaining spread of an effective gene drive product release. Subsequently, the development and testing pipeline for this technology is complicated by the fact that there is currently no broadly agreed upon procedure for carrying out testing involving environmental release which might not, for all practical purposes, amount to a full-scale deployment of the application.

The tricky reality of a gene drive is that its essential purpose is to self-propagate. This, indeed, is central to gene drive's unique usefulness, efficiency, and economy, but also makes controlling it more challenging. Particularly in low-threshold drive mechanisms (i.e., requiring fewer released organisms to initiate sustained spread) which have not been designed to be self-

limiting either geographically or generationally, it is plausible such a gene drive could spread as far as the species it is designed to affect is found. The mosquito species *Anopheles gambiae*, which is the vector responsible for the vast majority of malaria incidence in Africa, are endemic to much of the African continent. At the time of writing there are proof of concept lab experiments demonstrating successful population suppression of *Anopheles gambiae* in the lab using low threshold gene drive mechanisms (Kyrou et al., 2018; Simoni et al., 2020). But there are not yet any established methods for halting or recalling the spread of these organisms if they were to be released into the open environment amongst wild types of their species. There is work being done on various methods to control and limit the environmental spread of released gene drive organisms (Noble, 2016), and even applications to disable or reverse the effects of a released gene drive (*Safe Genes*, n.d.; Xu et al., 2020). However, as of yet there are no published proof-of-concepts for any of these gene drive control, limit, or reversal applications for malaria vectoring mosquitoes, and much of the work remains theoretical or in early stages of research and development (Bier, 2022). Even if proof-of-concepts in the lab existed, they would face the same testing issues faced by the first environmental release of an initial gene drive modified product.

This novel and potentially powerful field of research and development catalyzed a flurry of work in ethics, and the social sciences more broadly, to establish best practices and "societally acceptable rules of the road" (Adelman et al., 2017) for this novel technology which holds promise to yield enormous benefits to humanity if used responsibly. In 2016 the National Academies of Sciences, Engineering, and Medicine released a report calling for ethics scholarship as one of the important pillars for the success of gene drives (National Academies of Sciences, Engineering, and Medicine, 2016). The successful introduction of gene drive

technology will depend in large measure on getting the science and governance – ethics, risk assessment, regulation, politics, and stakeholder engagement – aspects right, and doing so the first time. If the first deployment of this technology goes awry it is likely to be a very long time before public opinion, let alone authorities and oversight bodies, will allow another attempt.

At the outset, given the public health outcomes being targeted by gene drive mosquito funders and developers (i.e. reduction of malaria incidence), the frame of reference and comparison for considering ethical questions for the technology quite understandably began from a medical and clinical frame of consideration. In response to questions about hypothetical future scenarios like 'who ought to decide whether to release gene drive mosquitoes?' many people's first instinct was to look to medical ethics norms and literature for guidance and precedent. Naturally, the issue of informed consent; how to conceive of and achieve it for a gene drive mosquito public health research project, rose to the forefront of the ethical discourse around this technology (Moloo, 2018; Singh, 2019; Smolenski, 2015, 2019). However, it was persuasively argued by Kolopack and Lavery that the clinical model of individualized informed consent was neither appropriate, ethically required, nor practicable in the gene drive mosquito as public health tool use case (Kolopack & Lavery, 2017). The ethics discourse pivoted to focus instead upon stakeholder and community engagement as a potential avenue for fulfilling obligations of procedural justice, and obtaining political and ethical legitimacy to proceed with gene drive research, particularly if it would involve a release of gene drive organisms into the shared environment (de Graeff et al., 2021).

It is intuitively understandable to turn to stakeholder and community engagement as a mechanism by which to obtain legitimacy for research and interventions which necessarily would affect a group of people, none of whom could opt out individually if a release of gene

drive modified mosquitoes occurred. The part of community engagement which informs communities about the relevant technology and method of intervention mirrors the informing aspect of the mechanism of individualized informed consent. And if individual informed consent seems hypothetically ideal, but practically impossible in this case, then what if we could get consent somehow from the group as a whole? In fact, some public health interventions are legitimated through processes such as this, for instance the obtaining of community-wide consent or authorization as seen in mass drug administration or cluster-randomized trials. Indeed, seeking consent in one form or another is the most common mechanism of legitimation within public health practice.

But gene drive mosquitoes as a public health intervention, if released, are expected to spread to an area far greater than that occupied by a single community, or even a cluster of several communities. The challenges posed by the potential for broad geographic, including international, transboundary spread of gene drives post-release, and subsequent ecological and environmental impacts began to be appreciated on an international scale. Calls and petitions for global-level governance, including for instantiation of a moratorium on uncontained use of all engineered gene drive organisms, were lobbied for in several forums of international governance (Callaway, 2018; Foote, 2020; Kelsey et al., 2020; *Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13*, 2016; *Texts Adopted - COP15 to the Convention on Biological Diversity (Kunming 2020) - Thursday, 16 January 2020*, 2020; Synbiowatch, 2016). As it stands, the ethics discourse appears conflicted between prioritizing localized loci vs. a global locus of deliberative gravity regarding governance of engineered gene drive technology. Local governance gives us contextualized deliberation and the closest proximate political deliberative level to that of individualized consent. Global governance encompasses and

considers (at least ideally) all constituencies, but being so broad and all-encompassing, it loses touch with the local and contextualized needs of individual communities, nations, and perhaps even whole regions. Recommendations have been forwarded with the intent to bridge the chasm between these two extremes, the local and the global, to create novel political deliberative and coordination processes (Kofler et al., 2018). I will provide an analysis of one prominent set of recommendations of this kind, from Kofler et al., in a later section. However, given their untested nature, somewhat broad strokes articulation, and very early-stage theoretical nature, it remains unclear whether these mechanisms are realistic, feasible, and capable of accomplishing the task of bridging such disparate levels of political organization as the local and global. Novel near-global or international governance structures seem a particularly unlikely possibility given how long new governance mechanisms take to establish at the global intergovernmental level (Kelsey et al., 2020), the speed at which gene drive technology is advancing, and the pressing and tragic nature of several major problems these technologies appear to represent promising solutions for.

In the sections that follow, an analysis is offered which considers the merits of several existing levels of political organization with regards to their appropriateness, or degree of legitimacy, as the primary locus of deliberation for release of gene drive technologies. This analysis acknowledges facts sometimes overlooked in recommendations made regarding gene drive technology. For instance, that ‘engineered gene drive’ names a broad category of technologies which can be utilized in various possible organisms, applications, and contexts; environmental, economic, sociocultural, and political. Each iteration of engineered gene drive product and paired context for release will require case-by-case assessment and deliberation. In light of these considerations, the author will analyse various levels of political organization in

relation to their capacity to offer a legitimate locus of deliberative gravity regarding the question of whether to conduct a gene drive product release; including for field testing purposes. The result of this author's analysis is to identify that, in most cases, the nation-state level of political organization as the most ethically appropriate, and therefore legitimate, locus of deliberative authority for a gene drive technology release decision given the existing geopolitical circumstances and available institutional actors and mechanisms.

Some qualification to this conclusion should be made on a case-by-case basis accounting for the reasonably expected geographic spread of a given population of gene drive organisms. If a gene drive application is expected to spread beyond the boarders of the nation-state which would choose to release it, that nation-state bears, at a minimum, the ethical obligation to consult with nation-states whose geographic territories are co-extensive with the reasonably predicted geographic spread of the gene drive organisms in question. The deciding nation-state may thus be pragmatically, and perhaps most often appropriately, constrained in their decision by the complex realities and pressures of international relations and commitments. However, the final decision whether to release an engineered gene drive organism should rest with a sovereign nation-state. A nation-state is best positioned and resourced to be responsive to considerations of international relations and responsibilities while simultaneously being informed by and prioritizing the interests of its constituents. While this author advocates for a state-level locus of decision making, for the purposes of coordination and cooperation, an international or global level gene drive monitoring system, perhaps including a voluntary universal registry of all gene drive releases, appears useful and prudent.

3. Inadequacy of Individual Consent Models

Given that environmental testing of gene drive mosquitoes will necessarily be attended by unique (or at least exceedingly rare) challenges which are not faced by most novel technologies (i.e. indefinite self-proliferation across geographic boundaries and time), contemplating a testing pathway for such applications reveals regulatory and jurisdictional gaps, or at least open questions, relating to governance of the technology. As such, there is an active international debate taking place about whether and how release for environmental testing of gene drive mosquitoes ought to be ethically and legitimately authorized. Gene drive mosquito applications under development for the purpose of malaria elimination were initially approached by some through the most common health ethics lens; that of clinical medical ethics. Within this paradigm one of the highest values is that of individual autonomy of the patient or research participant. The gold standard ethical mechanism for protecting and preserving this autonomy is the practice of obtaining individual informed consent from every person whose interests may be directly affected by actions, procedures, or interventions of medical or research personnel. With few exceptions, in a clinical setting maintaining this standard is the correct and ethically sound course of action.

However, rather than viewing gene drive mosquitoes for malaria elimination through the lens of clinical ethics, it is more accurate to conceive of them as a public health intervention upon the environment with the intention of making the environment a healthier place for its resident human population. You might say they amount to a method for inoculating the environment rather than individuals. As Nancy Kass put it in "An Ethics Framework for Public Health,"

> Codes of medical and research ethics generally give high priority to individual autonomy, a priority that cannot be assumed to be appropriate for public health practice … public

> health seeks to ensure societal conditions under which people can lead healthier lives, minimizing threats to our health 'that can be averted or lessened only through collective actions aimed at the community'. (Kass, 2001, p. 1776)

Gene drive mosquitoes released into the environment are expected to have no direct effects on the resident human population. In particular, use of a driving Y-chromosome population suppression drive like the one being developed by Target Malaria would ensure that people are not bitten by gene drive mosquitoes since only male mosquitoes would carry the gene drive, and male mosquitoes do not bite.[3] Despite this, some ethics commentators have suggested that the requirement of individual informed consent should play a role in legitimating gene drive mosquito trials (Resnik, 2014). This author disagrees with that stance however, and aligns instead with the opinion of Kolopack and Lavery in their article, "Informed consent in field trials of gene-drive mosquitoes", which scrutinizes the ethical necessity of individual informed consent in field trials of gene drive mosquitoes (Kolopack & Lavery, 2017). After surveying the literature and international guidance documents regarding the definitions of human research subjects, they state:

> Living in the vicinity of a release trial does not automatically render someone a research subject and therefore it is inappropriate to require informed consent from every individual in the vicinity simply because the technologies being deployed are still in their testing and development stages. Arbitrarily requiring informed consent from every individual and household in geographic proximity to a release trial misrepresents and undermines the value of informed consent in research and establishes worrisome precedents about the appropriate application of research ethics policies and procedures. (Kolopack & Lavery, 2017)

They concluded that, apart from some practicably separable periphery research activities, a gene drive mosquito field trial does not in essence involve human subjects, and thus does not ethically demand individual informed consent of every individual or household proximate to the release or

[3] Only female mosquitoes take blood meals. They use the protein and iron found in blood to grow their eggs.

eventual geographic spread of the gene drive mosquitoes. Not only is individual informed consent ethically unnecessary, but, "It also raises potentially insurmountable logistical challenges that will ultimately impede important science, with no clear ethical rationale" (Kolopack & Lavery, 2017).

Kolopack and Lavery's paper focusses narrowly upon the role of individual or household-level informed consent in relation to gene drive mosquito environmental testing. They deny its requirement for an environmental release of gene drive mosquitoes and provide some related exceptional circumstances under which individual informed consent should still be the standard. They subsequently mention very briefly the importance of giving attention and effort to the challenges of regulation and stakeholder engagement relating to gene drive technology. Yet, while they have explained why it is safe to eliminate individual informed consent as the source of authorization for gene drive mosquito environmental release, they make no attempt to offer an alternative source for ethical authorization of a release. In addition to establishing ethical regulations and stakeholder engagement practices relating to gene drive mosquito release trials it remains important to establish who has, or at what level of political organization there exists ethical justification to issue or withhold legitimate final authorization to release gene drive mosquitoes into the environment.

4. Inadequacy of Community Consent or Authorization

We have seen that individual consent, as in the clinical medical model, is inappropriate and impracticable to the task of legitimizing a decision to conduct an open release of gene drive modified mosquitoes. But gene drive modified mosquitoes certainly do not represent the only or first public health intervention for which individual consent was inappropriate or impracticable

to the purpose. The history of public health interventions offers many examples of community-wide interventions – e.g., mass drug administrations (MDA) and cluster-randomized controlled trials (CRT) – where, for various reasons, consent was not sought from individuals, but instead sought from a community leader, or community representative. In some cases, this was done for socio-cultural reasons. For instance, in certain indigenous, tribal, and/or religious communities in which, by their own social mores, it is appropriate for a leader/s to consent on behalf of the group, and would be inappropriate for individuals to consent for themselves. This approach has its ethical pros and cons. On the one hand, it acknowledges that it is inappropriate for cultural outsiders (e.g., scientists and medical personnel from the global north) to dictate how a traditional community from a different part of the world deliberates, governs, and authorizes certain activities. On the other, there are strong arguments that any form of government which lacks democratic principles is inherently illegitimate. Additionally, input into a deliberation from minority and marginalized groups within such a community tends to be absent. Recently there have been attempts to bridge this ethical dichotomy by some groups engaging traditional communities around participation in community-wide research activities. For instance, Target Malaria, a research consortium developing gene drive modified mosquitoes for malaria elimination, operating on the principle of co-development worked with local communities to establish an Ethics Advisory Committee and mutually agreeable community acceptance model for whether to proceed with proposed research activities (Roberts & Thizy, 2022).

There is broad agreement amongst commentators (George et al., 2019; Kofler et al., 2018; Moloo, 2018; Neuhaus, 2018; Thizy et al., 2019, 2020, 2021) and guidance documents (*Convention on Biological Diversity*, n.d.; James et al., 2018; Long et al., 2020; National Academies of Sciences, Engineering, and Medicine, 2016; World Health Organization, 2021)

that some form of local or community consent, authorization, or agreement is integral to legitimate authorization for release of gene drive mosquito applications, even for testing. Admittedly, some of these are fairly ambiguous as to precisely what they take obtaining community consent to involve. To the degree they suggest that community consent must be sought *qua* meaningful feedback and input from local communities which is weighed and integrated into the process of a higher order deliberation, then this author agrees. Processes for soliciting and enabling meaningful integration of voice and participation from local communities in national-level deliberation is no doubt extremely important and manifests core democratic principles. This is the role I see for bi-lateral, broad, and authentic community and stakeholder engagement activities.

I do not conceive of such processes as constituting consent seeking, nor, as Kolopack and Lavery pointed out, is it reasonable to expect to obtain consent *per se* via these processes. Though in a similar fashion to consent seeking, community and stakeholder engagement processes do honour the deeper principle of respect for persons and their autonomy, they do not constitute a full surrogate for consent. They may present the best way of informing communities and broader publics about possible or planned gene drive interventions, and in turn for those in research and governance roles to perform local knowledge engagement (Hartley et al., 2019) and be informed of local values, perceptions, preferences, and needs.

The concept of consent includes the idea that someone in a position to give or withhold consent has justified authority to answer in the negative or affirmative regarding the question of whether some other agent/s may proceed in some specific fashion in relation to the first agent. In the case of gene drive mosquito applications likely to affect the environment of much of the African continent (however severely or mildly), local communities do not hold the kind of

justified authority that grants the right to give or withhold authorization for at least the following two reasons.

First, because the question is about the interests of a *far* larger constituency than any single community, or even cluster of communities. To the degree consent of the governed is ethically important in legitimizing a political decision, it is important that all members of the constituent population have the opportunity for input. Seeking community consent might make a lot of sense in the case of a gene drive application for use in an isolated species population which resides exclusively alongside one or a handful of communities, or for localized research activities like mosquito collection, and epidemiological surveillance. However, it does not make ethical or practical sense when considering the governance of gene drive applications in a species such as *Anopheles gambiae*; a species population which is not small nor isolated, but has a population reaching across much of the African continent. This becomes a grander issue than local communities can legitimately claim deliberative authority over when you consider that a single small-scale release of even a few gene drive modified mosquitoes could reasonably be expected to spread the gene drive through the genome of the entire continent-wide species population[4]. Legitimacy requires some contextually appropriate form and level of consent of those who would be affected by a political decision, but other criteria for legitimacy are as important or more so. Thus, as O'Neill has convincingly argued, consent in some degree is necessary, but it is not sufficient (O'Neill, 2002, 2003, 2016).

Secondly, if we consider that in addition to consent, another criteria for the legitimacy of a deliberative body is the rationally expected increased probability of beneficial consequences

[4] Though modelling suggests several variables which might halt the drive mechanism's spread of the selected genetic alteration before it reached fixation in the entire continent-wide *Anopheles gambiae* population.(Beaghton & Burt, 2021; Eckhoff et al., 2017)

based on their deliberation, then we must take into account the highly technical, expertise-requiring aspects of the decision to release gene drive modified mosquitoes. As Habermas puts it: "Deliberative politics acquires its legitimating force from the discursive structure of an opinion- and will-formation that can fulfill its socially integrative function only because citizens expect its results to have a reasonable *quality*." (Habermas, 1996, p. 304) Through engagement, communities may gain some insight and understanding into the broad strokes workings of gene drive molecular mechanisms, the planned research activities and desired outcomes of a gene drive mosquito release. However, it is experts – scientists, regulators, risk assessors, systems modelers, etc. – who are most knowledgeable, best prepared, resourced, and positioned to make rational, empirically-based assessments and predictions about the results of a gene drive mosquito release. Generally, experts of the relevant kinds are employed by national governments and operate in their roles at this political level; not, in most cases the political level of a local community. To the degree that it can be argued every expert belongs to one community or another, I would further point out that without the institutional capacity to gather, fund, and coordinate the efforts of the relevant and necessary diversity of expertise and their respective analyses towards deliberation about a release, individual experts are not so useful on their own or in small groups for making appropriately informed recommendations about matters of the scale presented by a gene drive environmental release.

In fact, the idea of seeking community consent for release of gene drive modified mosquitoes begins to look as irrational and logistically impossible as seeking individual informed consent. Afterall, there are many hundreds, or thousands, of distinct communities across the continent of Africa which might be affected if gene drive modified mosquitoes were to be released towards the goal of malaria elimination. It is on these grounds and at this stage of the

analysis that I suggest elimination of the local community level of political organization as an ethically viable locus of legitimate authoritative decision making for whether a gene drive modified *Anopheles gambiae* release for malaria elimination in Africa ought to proceed.

5. Inadequacy of global-level decision making as locus of gene drive release decision

If a legitimate authoritative body will ideally take inputs into its deliberations from a constituency which includes all those who may be affected by the results of their decision, then let us consider candidate institutions which govern at the global, or at least broad international level. Thus far it seems none of the published guidance documents have been explicitly attempting to locate the appropriate level of political organization at which a final decision whether to release gene drive mosquitoes ought to be made and were rather attempting to point to ethically ideal (sometimes necessary) aspects of the process of deliberation and to groups whose interests should be considered in the course of those deliberations. In doing so, they place their emphasis heavily on procedural justice concerns. They variously weight the value of the community level or the global governance level higher in their accounts, while acknowledging the value of both, yet never explicitly locating the political level at which the decision ought to finally be made. No doubt, deliberation on this matter should include consideration of inputs from local and global intergovernmental levels of political organization. But the question of legitimate deliberative gravity – from where should the final decision be sought, and how should actors deliberating at that level of political organization weigh the various inputs and opinions under consideration in their deliberation – is an important one for all involved, as anyone seeking to give input on the decision or seeking authorization for release of their gene drive mosquito application needs to know who to address for these ends. It is also important to know who can be

held responsible for the consequences of such a decision. Some form of deliberative centralization or primary locus of decision making is necessary to deliver a final decision on whether to proceed with a release.

As I mentioned earlier, many of those who forward positions in favour of some form of community consent do so with some ambiguity as to what their proposal would amount to in concrete terms. In some cases, this ambiguity arises from the fact that in addition to community or local consent they also suggest the importance of global governance or oversight of that process. While most commentators and guidance documents appear, at least explicitly, silent on the question of where the proverbial deliberative buck stops, in "Editing Nature: Local Roots of Global Governance" a group of prominent scholars in the gene drive discourse, Kofler et al., recommend the creation of a novel global-level 'coordinating body' for governance of genetically edited organism release into the environment (Kofler et al., 2018). The coordinating body they outline would be responsible for, among other things, establishing and facilitating a global deliberative framework and nominating local leadership from communities expected to be effected by a given gene editing intervention who would share "ultimate control over the deliberative process" (Kofler et al., 2018).

In its theoretical and somewhat vague form, the proposal forwarded by Kofler at al. seems an excellent, if roughly outlined, model for maximizing procedural justice for local and marginalized communities in a regime of global governance, but the authors themselves acknowledge some very serious unresolved challenges to implementing such a model:

> Important questions remain to be answered: How can deliberative procedures effectively weigh local benefits with more-widespread global risks? How would transfer of control for the deliberations to local leaders take place? What structures are in place to guarantee historically marginalized voices are heeded in deliberation? What institutional procedures and evaluation mechanisms are needed to ensure accountability?(Kofler et al., 2018)

In addition to these concerns, this author wonders at the likelihood of such an international body ever being created or funded given the manner in which it appears inclusive of local and global jurisdiction, while leapfrogging any meaningful inclusion and input from national-level jurisdiction. Given the extant global historical and geopolitical circumstances we find ourselves in – where nation-states are sovereign, control legal and regulatory systems, economies, and a monopoly on force – this model seems highly idealistic; even utopian. In its attempt to maximize for consent and procedural justice, which are necessary but not sufficient for legitimacy, it fails to take into account political and economic realities, thereby risking unduly high likelihood of failure to realize substantive justice ends of bringing about beneficial consequences. If the world waited to use, or even test, any application for the genetic editing of nature until such a governance model were in place and functioning it would probably take many years, even decades, in the unlikely situation where such a model is accomplished at all. In the meantime, an enormous magnitude of harm and injustice will have accrued in situations where novel genetic technologies could have provided options for significant levels of alleviation where no others currently exist, including in the work of global health and environmental conservation. The case of gene drive modified mosquitoes for malaria elimination being just one prominent example in which the status quo sees an estimated 241 million human malaria cases and 627,000 malaria deaths worldwide in 2020 (*World Malaria Report 2021*, 2021). Since 2015 there has been no significant decline in malaria incidence nor deaths (*World Malaria Report 2021*, 2021). Our current methods for fighting the spread of malaria – drugs and insecticides – are quickly losing efficacy as their targets develop resistance to them. Humanity needs new and innovative tools in order to maintain, let alone continue making progress in our fight to end malaria (World Health Organization, 2020).

International governance bodies and conventions have much to offer in terms of providing fora for development and dissemination of guidance and capacity building regarding regulatory and risk assessment processes and best practices, and for discussion and consensus building around how best to manage international expectations, relations, and monitoring, and establishing agreements around liability and redress regarding field testing and use of engineered gene drive applications. However, ultimately, in our existing global order nation-states remain sovereign and are ethically, and most often legally, obligated to act in the best interests of their own people (of course, with consideration for foreign relations since these too will inevitably affect their people). It is at the state-level that decisions are made regarding international relations such as whether to sign onto a given international agreement, and whether to remain in or to withdraw from one previously agreed to. As stated by António Guterres, Secretary-General of the United Nations, in a July 2020 open letter, "Today's multilateralism lacks scale, ambition and teeth — and some of the instruments that do have teeth show little or no appetite to bite, as we have seen in the difficulties faced by the Security Council." (Guterres, 2020) It relies on the behaviour and enforcement of ostensibly peer nation states which are each primarily and finally responsible to the interests of their own constituents, and between which there are obvious and severe power imbalances. This poses problems of justice and fairness when policies and regulations are issued in international level fora, for instance, to all signatories of the UN's Convention on Biological Diversity (CBD), that would bar or place major obstacles in the way of some nations taking calculated risks, e.g., on a gene drive intervention for malaria elimination. The risk calculation for countries which see gene drive technology as an opportunity to improve the health and living conditions of their constituents will be very different from those for whom the domestic status quo is acceptable, so any risk seems unacceptable. Even if a majority of

nation states were to decide democratically to sign a treaty globally banning or placing a moratorium on gene drive technology release due to uncertainty and risk posed by a novel technology in order to protect their comfortable status quos from any additional risk, the quasi-democratic process of voting nation states would not be sufficient to legitimate on the ongoing suffering, harm, injustice, and death persisting as the status quo in the minority of nation states where the risk calculation regarding gene drive looks very different, and much more favourable towards use of the technology.

As was demonstrated most clearly in the last couple of years as the world faced the scourge of a global pandemic, the world failed to enact just global vaccine distribution. The Review Committee on the Functioning of the International Health Regulations during the COVID-19 pandemic had the following to say about their performance and enactment by the global community's nation-states:

> … much of what is in the IHR is well considered, appropriate, and meaningful in any public health emergency. However, many countries only applied the IHR in part, were not sufficiently aware of these regulations, or deliberately ignored them and that WHO did not make full use of the powers given to it through the wording and spirit of the IHR. Thus, the IHR are not deficient, but their implementation by member states and by WHO was inadequate. (Aavitsland et al., 2021)

Even when unselfish, global coordination was objectively evidenced to be in the best interest of all nations, our contemporary global-level governance and coordination mechanisms failed to achieve just outcomes in the face of fear and insular, short-sighted national interests. Without some higher-level authority or coercive power capable of enforcing compliance, global-level governance, while useful for promoting global coordination when all parties see it as in their best interest, quickly fails when they do not. How then can we expect these same systems to yield a fair playing field and just results for the less wealthy and powerful nations most afflicted by

malaria, particularly when most other countries involved in the deliberation, and arguably wielding greater influence on global policies and legislation, are not currently at risk to malaria. Many powerful nations thus see novel gene drive interventions not for the vitally needed benefits they may yield, but only through the lens of risk mitigation. The precaution of 'better safe than sorry' only applies if one is already safe. Calling for global-level governance of a technology which, while posing some uncertainty of minor ecological risk, could save many millions of human lives in a large region of the world, but does not seem to have immediate or important application in many other parts of the world amounts to an imperialistic imposition and insistence on control which betrays a lack of trust in and respect for the African states which wish to fully investigate this technology as a possible game changing tool for use in their age old war with a deadly pathogen and its vectors (*Gene Drives for Malaria Control and Elimination in Africa | NEPAD*, n.d.). As Buchanan and Keohane said, "Legitimacy disputes concern not merely what institutional agents are morally permitted to do but also whether those to whom the institution addresses its rules should regard it as having authority." (Buchanan & Keohane, 2006) Consider the following scenario; the CBD, following the calls of over 160 NGOs and civil society groups (*Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13*, 2016), and the policy directions of many nation states, most notably those of the European Union ("European Parliament calls for ban on gene drive technology," 2021), issued an indefinite global moratorium against the release of gene drive modified organisms into the wild by any parties to the CBD. Should African nations view a CBD rule which would bar the possibility of exploring gene drive as a malaria elimination tool as legitimate? I, for one, think not. Remember, the eradication of malaria would annually save nearly half a million of their people's lives and an immeasurable amount of suffering of the more than 200 million people who contract malaria

every year, not to mention the immense economic cost of all of this morbidity and mortality which further exacerbates difficulties of development.

6. Why state-level locus of deliberative gravity for political authorization of gene drive release is most ethically justified

The nation state-level is the ethically appropriate level of political organization to deliver legitimate political authorization for a decision whether to release gene drive modified organisms; particularly for gene drive modified mosquitoes for the purpose of malaria elimination in Africa. As has been demonstrated, this conclusion is to some degree arrived at through a process of elimination rather than by finding all attributes of ideal legitimacy in the institution of a nation-state. The other available options are thoroughly unsatisfactory. Nevertheless, given the non-ideal reality of our world, the nation-state is attended by several characteristics which will make it, in most cases, the most ethically suitable locus of deliberative gravity for a release decision pertaining to gene drive modified organisms. As this would be a political decision with effects at least on a national level, and likely extending to an international level, the final decision should be made, and responsibility for it held, by a nation-state. There are several reasons for believing this is the case. In our contemporary geopolitical context, it is at the state-level that the highest concentration of political power and responsibility exists. The state-level is typically also the political level at which institutions with assigned regulatory jurisdiction, the most resources, and expertise exist for properly assessing and addressing the risks and regulatory issues surrounding gene drive mosquito applications (Kelsey et al., 2020; Warmbrod et al., 2022). For instance, regulatory agencies, particularly for health, environmental protection, and agriculture; three likely fields of influence for gene drive technology, tend to

operate at the national level in the majority of countries in the world (Kelsey et al., 2020). When compared to international governance structures, the state-level has more political potency and legitimacy as all contemporary states exist (at least ostensibly) to operate in the interests of their constituent populations.

Of course, in a final sense, responsibility for a state's political legitimacy lies with that state's political gate keepers, and can vary significantly from one nation-state to the next. But it is safe to assume the idiosyncratic governance challenges posed by gene drive technology will not singlehandedly catalyze a rapid transformation of all less-than-democratically-legitimate states into firmly legitimate ones. The task of this paper is to identify the, generally, most ethically justified available option. It is not helpful to demand an ideal situation exist before any decisions can be made; ideal circumstances are not real. In general, state sovereignty offers the most potent and legitimate political level from which to grant both internal authorization and to consider foreign policy and make international political agreements. Nation-states tend to have established and culturally appropriate processes for accessing, balancing, and integrating the interests and input of their constituents. In democratic societies, the most obvious example of this is the process of holding regular democratic elections in which the citizenry vote for and elect their political leadership from amongst their own ranks, thus representing at least the majority values of the relevant constituency in the selection of leadership. The nation's leaders then have a mandate to act in accord with the values they advertised in order to win the last election as they wield the powers and resources of the state to serve the interests of the state's constituents. In addition, if exceptionally contentious political issues arise, referendums may be held in which populations have the opportunity to vote directly on the state's policy response to the issue at hand.

Perhaps most importantly, it is the national governance level at which the best balance is struck between the contextualized concerns of constituent individuals and communities at the local level and the interests of other countries at the international political level (which of course represent other local peoples and communities). It is nation-states which have existing mechanisms and processes, such as state-level ministries of foreign policy or global affairs, for managing and balancing these bivalent constellations of duties. In fact, to the degree we have international or global-level governance, it is *qua* the voluntary, self-interested cooperation of states and their dedicated diplomatic agencies and institutions. As Fidler describes in "Health as Foreign Policy: Harnessing Globalization for Health" (Fidler, 2006), states engage in foreign policy to fulfill four basic governance functions: (1) "states seek to ensure their security from external threats"; (2) "a country uses foreign policy to contribute to its economic power and prosperity"; (3) "to support the development of political and economic order and stability in other countries"; (4) "states make efforts to promote and protect human dignity through foreign policy". To the degree that the world has international treaties, regulations, and a shared legal system, it is through the voluntary participation of sovereign nation-states. So if we identify and assign the locus of deliberative gravity for decision making for open release of gene drive modified organisms to nation-states, they have existing ministries and mechanisms for adjudicating not only the interests of their constituents, but also for taking into account international relations, and existing norms and agreements. Of course, by their nature and design, they will prioritize the interests of their own people, but so will every other country. Thus, from the threads of tension between the self interest of each against the self interest of the rest, is weaved the diplomatic, trade, global development, and peacekeeping safety net against open conflict and war most of the world has come to enjoy in most places, most of the time, since at

least the end of the Cold War (~1990) (Rittberger & Fischer, 2008). The point being, more and more, nation-states make domestic decisions with greater sensitivity to the effects of those decisions on global neighbours. Even if they do so out of self-interested fear of sanction, it creates and fosters a global atmosphere of cooperation while maintaining in decision making the potency of the contextualized interests of each country's constituents.

It may be claimed that I am placing too much faith in the legitimacy of state power, or at least over-generalizing how frequently states legitimately and properly represent the interests of their constituents. I fully acknowledge my broad and general claims regarding state legitimacy are ultimately context dependent and contingent. There are entire disciplines dedicated to examining political legitimacy and this analysis, in its broad and general approach, misses the depth of analysis that a contextually rich case analysis could offer. But in relation to the question I am aimed at answering in this paper; in general, from what level of political organization is it ethically appropriate to seek authorization prior to releasing mosquitoes engineered with a gene drive for the purpose of malaria elimination, the state-level strikes the best and most ethically authoritative balance in a set of less than ideal options which otherwise include individual persons, local communities, or some manner of global or international governance.

7. A proviso rooted in the nature of a gene drive's expected geographic spread

Up until now this analysis has focussed upon the question of appropriate political legitimacy mainly by considering features of each level of political organization and identifying the level which seems best suited to address the general 'size' of the effect space of a gene drive product environmental release. I have done so by identifying the broadest level of political organization with enough political legitimacy, resources, and appropriate mechanisms and

motivations for addressing the question with sensitivity to both domestic context, as well as global relations. I believe this centre of deliberative gravity belongs at the nation-state level. But there is another relevant variable which will meaningfully inform an appropriate identification of what might be considered, in contrast to the center of gravity, the external bounds for the locus of political deliberation. A variable which makes the most appropriate extent of the deliberation space international without being global. This variable is the expected geographic spread of a given gene drive organism according to the best scientifically informed predictions. There are several forms of gene drive mechanism under development, and several of them are being developed to have self limiting spread, or to be released in a location where environmental features are expected to limit spread. However, some of the gene drive modified organisms most well funded and advanced in development, particularly gene drives meant for malaria elimination goals, are designed to spread as far and wide as the wild target species is found. This means, if they function as they are expected to, they will spread beyond the national boarders of any country in which they are released.

I have argued that the locus of deliberative gravity and authority for a final go/no go decision should belong to a nation-state, and I maintain this view. Yet, in the interest of consent and democratic approval, the space of political deliberation will ideally be distributed across the jurisdictions of the nation-states geographically co-extensive with the endemicity of the species which is the target of the engineered gene drive in question; or at least as far as the gene drive spread is expected to geographically extend. In concrete terms, if a state is considering utilizing a gene drive application to achieve, for instance, suppression of their resident population of malaria plasmodium vectoring mosquitoes, and the gene drive modified mosquitoes are expected to spread into neighbouring national territories, the first state ought to consult with the

governments of the territories where spread is expected, attempt to come to an agreement about the environmental release of gene drive modified organisms, and create a coordinated effort towards mutually beneficial outcomes and monitoring of the effects of the intervention. An example of this kind of consultation and coordination is displayed by the African Union Development Agency (AUDA-NEPAD) and the West Africa Health Organization (WAHO) serving as Secretariate to the West Africa Integrated Vector Management (WA-IVM) Steering Committee. WA-IVM held a meeting with member states in December 2021 in Accra, Ghana. Among other objectives, the meeting sought to, and did adopt the first set of guidelines, developed through a comprehensive process started in 2018, to guide regulators and scientists undertaking research activities towards the development of gene drive technologies as a novel malaria vector control tool (*WA-IVM Steering Committee Adopts Guidelines for Genetically Based Control of the Malaria Vector | AUDA-NEPAD*, n.d.). Through regional coordinating bodies for the African continent, representatives of African nation-states negotiated and adopted shared guidelines for proceeding with gene drive research in their respective countries.

To consult other potentially affected nations and attempt to cooperate towards the best interests of all is ethically ideal, and should always be sought out, because the most ethically legitimate decision will be informed by some contextually appropriate level of consent and democratic approval. This ideally will be achieved by including in the deliberation the governments of all affected geographies. But we live in a non-ideal world, and sometimes governments will be able to negotiate their way to agreement on a shared way forward. IN cases such as these, the most ethical option available may, nevertheless, not meet the standard of the ideal. I do not believe this ethical ideal-motivated diffusion of deliberative gravity dilutes a sovereign nation-state's authority to the point that other potentially affected states deserve an

authoritative veto over the first state's release decision. If a nation-state's analysis reveals that its constituents will derive greater benefit, all things considered, from pursuit of the engineered gene drive release than they risk suffering from the long-term international political fallout of having acted against neighboring states wishes, there remains a strong ethical mandate to proceed with the release. This is because even if the degree of procedural justice achieved under these circumstances is sub optimal since the entirety of the potentially affected constituency is not represented to an ideal degree in the decision, if a nation state nonetheless assesses that a gene drive modified mosquito release will be of great enough benefit to its constituents that it outweighs the assessed potential political and environmental fallout it causes, then for the sake of achieving substantive justice, and given the state's sovereignty, and special obligation to its own constituents interests, it stands to reason the state may have an ethical obligation to proceed with the release. The circumstances where such a decision is ethically justified are likely to be extremely rare, but it seems important to identify that they could in principle obtain. Beneficial outcomes, if great enough in magnitude, can mitigate against the required degree of perfection in the normative requirement for consent and democratic approval in the assessment of legitimacy.

8. Conclusion

If you agree with the analysis presented here, then I have shown that a decision to release gene drive mosquitoes into the environment for the purpose of malaria elimination in Africa ought to, in a final sense, be made at the state-level. Seeking merely individual informed consent or community consent result in similar ethical problems of severely limited scope of justified authority relative to the enormous political scope of the issue and consequences at hand in such a decision. Nonetheless, it is vitally important that potentially affected people be provided the

opportunity to engage in transparent and meaningful bi-lateral processes which provide authentic opportunity for input in the process of deliberating about and shaping such an intervention. Political gatekeepers are ethically responsible for ensuring such processes are in place and appropriate engagement activities are undergone on the way to deliberation.

On the other extreme of the political spectrum, global-level international governance structures are too politically diffuse and subject to the more potent political force, and focussed political interests of their constituent states, particularly wealthy and powerful ones, to provide the most legitimate and authoritative platform for a decision whether to release gene drive mosquitoes into the African environment for the purpose of malaria elimination. Even so, they do provide important platforms for sharing information, best practices and guidance regarding regulation, and risk assessment, and perhaps for monitoring of global gene drive release events and spread.

Having reasonably eliminated all other levels of political organization at which to legitimately and authoritatively rest the mantle of the deliberative center of gravity for the question whether to release gene drive modified mosquitos on the African continent for malaria elimination, it seems reasonable to conclude that the nation-state level represents the most politically legitimate, potent, balanced, relevant and epistemically privileged point of view for making such a decision, and therefore possessing the most ethically justifiable authority to do so, generally speaking. This conclusion is tempered by the proviso that the expected geographic spread of a gene drive technology confers obligations upon a state considering such a release to consult with and aim to coordinate and cooperate with other potentially affected states. These obligations, however, do not remove a sovereign nation-state's ethical mandate to ultimately

decide for itself whether to proceed with an engineered gene drive modified organism environmental release.

Works Cited for Chapter Four

Aavitsland, P., Aguilera, X., Al-Abri, S. S., Amani, V., Aramburu, C. C., Attia, T. A., Blumberg, L. H., Chittaganpitch, M., Duc, J. W. L., Li, D., Mokhtariazad, T., Moussif, M., Ojo, O. E., Okwo-Bele, J.-M., Saito, T., Sall, A. A., Salter, M. W. A. P., Sohn, M., & Wieler, L. H. (2021). Functioning of the International Health Regulations during the COVID-19 pandemic. *The Lancet*, *398*(10308), 1283–1287. https://doi.org/10.1016/S0140-6736(21)01911-5

Adelman, Z., Akbari, O., Bauer, J., Bier, E., Bloss, C., Carter, S. R., Callender, C., Costero-Saint Denis, A., Cowhey, P., Dass, B., & others. (2017). Rules of the road for insect gene drive research and testing. *Nature Biotechnology*, *35*(8), 716–718.

Alphey, L. S., Crisanti, A., Randazzo, F. (Fil), & Akbari, O. S. (2020). Opinion: Standardizing the definition of gene drive. *Proceedings of the National Academy of Sciences*. https://doi.org/10.1073/pnas.2020417117

Annas, G. J., Beisel, C. L., Clement, K., Crisanti, A., Francis, S., Galardini, M., Galizi, R., Grünewald, J., Immobile, G., Khalil, A. S., Müller, R., Pattanayak, V., Petri, K., Paul, L., Pinello, L., Simoni, A., Taxiarchi, C., & Joung, J. K. (2021). A Code of Ethics for Gene Drive Research. *The CRISPR Journal*, *4*(1), 19–24. https://doi.org/10.1089/crispr.2020.0096

Beaghton, P., & Burt, A. (2021). *Gene drives and population persistence vs elimination: The impact of spatial structure and inbreeding at low densit*. https://doi.org/10.1101/2021.11.11.468225

Beans, C. (2018). News Feature: What happens when lab animals go wild. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(13), 3196–3199. https://doi.org/10.1073/pnas.1803284115

Bier, E. (2022). Gene drives gaining speed. *Nature Reviews Genetics*, *23*(1), 5–22. https://doi.org/10.1038/s41576-021-00386-0

Buchanan, A., & Keohane, R. O. (2006). The Legitimacy of Global Governance Institutions. *Ethics & International Affairs*, *20*(4), 405–437. https://doi.org/10.1111/j.1747-7093.2006.00043.x

Burt, A. (2003). Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proceedings of the Royal Society B: Biological Sciences*, *270*(1518), 921–928. https://doi.org/10.1098/rspb.2002.2319

Burt, A., & Crisanti, A. (2018). Gene Drive: Evolved and Synthetic. *ACS Chemical Biology*, *13*(2), 343–346. https://doi.org/10.1021/acschembio.7b01031

Callaway, E. (2018). UN treaty agrees to limit gene drives but rejects a moratorium. *Nature*. https://doi.org/10.1038/d41586-018-07600-w

Convention on Biological Diversity. (n.d.). Retrieved September 12, 2018, from https://www.cbd.int/

de Graeff, N., Jongsma, K. R., Lunshof, J. E., & Bredenoord, A. L. (2021). Governing Gene Drive Technologies: A Qualitative Interview Study. *AJOB Empirical Bioethics*, 1–18. https://doi.org/10.1080/23294515.2021.1941417

Dutra, H. L. C., Santos, L. M. B. dos, Caragata, E. P., Silva, J. B. L., Villela, D. A. M., Maciel-de-Freitas, R., & Moreira, L. A. (2015). From Lab to Field: The Influence of Urban Landscapes on the Invasive Potential of Wolbachia in Brazilian Aedes aegypti Mosquitoes. *PLOS Neglected Tropical Diseases*, *9*(4), e0003689. https://doi.org/10.1371/journal.pntd.0003689

Eckhoff, P. A., Wenger, E. A., Godfray, H. C. J., & Burt, A. (2017). Impact of mosquito gene drive on malaria elimination in a computational model with explicit spatial and temporal dynamics. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(2), E255–E264. https://doi.org/10.1073/pnas.1611064114

Esvelt, K. M., Smidler, A. L., Catteruccia, F., & Church, G. M. (2014). Concerning RNA-guided gene drives for the alteration of wild populations. *ELife*, *3*. https://doi.org/10.7554/eLife.03401

European Parliament calls for ban on gene drive technology. (2021, June 9). *STOP GENE DRIVES*. https://www.stop-genedrives.eu/european-parliament-calls-for-ban-on-gene-drive-technology-2/

Fidler, D. P. (2006). Health as foreign policy: Harnessing globalization for health. *Health Promotion International*, *21*(suppl_1), 51–58. https://doi.org/10.1093/heapro/dal051

Foote, N. (2020, July 3). NGOs call for moratorium on controversial "gene drive organisms." *Www.Euractiv.Com*. https://www.euractiv.com/section/health-consumers/news/ngos-call-for-moratorium-on-controversial-gene-drive-organisms/

Gene Drives for Malaria Control and Elimination in Africa | NEPAD. (n.d.). Retrieved June 25, 2018, from http://www.nepad.org/resource/gene-drives-malaria-control-and-elimination-africa

George, D. R., Kuiken, T., & Delborne, J. A. (2019). Articulating 'free, prior and informed consent' (FPIC) for engineered gene drives. *Proceedings of the Royal Society B: Biological Sciences*, *286*(1917), 20191484. https://doi.org/10.1098/rspb.2019.1484

Gould, F., & Schliekelman, P. (2004). Population genetics of autocidal control and strain replacement. *Annual Review of Entomology*, *49*, 193–217. https://doi.org/10.1146/annurev.ento.49.061802.123344

Guterres, A. (2020). *Global Wake-Up Call*. United Nations. https://www. un. org/en/coronavirus/global-wake-call

Habermas, J. (1996). *Between Facts and Norms: Contributions to a Discourse Theory of Law and Democracy* (W. Rehg, Trans.). MIT Press.

Hammond, A., Pollegioni, P., Persampieri, T., North, A., Minuz, R., Trusso, A., Bucci, A., Kyrou, K., Morianou, I., Simoni, A., Nolan, T., Müller, R., & Crisanti, A. (2021). Gene-drive suppression of mosquito populations in large cages as a bridge between lab and field. *Nature Communications*, *12*(1), 4589. https://doi.org/10.1038/s41467-021-24790-6

Hartley, S., Thizy, D., Ledingham, K., Coulibaly, M., Diabaté, A., Dicko, B., Diop, S., Kayondo, J., Namukwaya, A., Nourou, B., & Paré Toé, L. (2019). Knowledge engagement in gene drive research for malaria control. *PLoS Neglected Tropical Diseases*, *13*(4). https://doi.org/10.1371/journal.pntd.0007233

James, S., Collins, F. H., Welkhoff, P. A., Emerson, C., Godfray, H. C. J., Gottlieb, M., Greenwood, B., Lindsay, S. W., Mbogo, C. M., Okumu, F. O., Quemada, H., Savadogo, M., Singh, J. A., Tountas, K. H., & Touré, Y. T. (2018). Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group. *The American Journal of Tropical Medicine and Hygiene*, *98*(6 Suppl), 1–49. https://doi.org/10.4269/ajtmh.18-0083

Kass, N. E. (2001). An Ethics Framework for Public Health. *American Journal of Public Health*, *91*(11), 1776–1782. https://doi.org/10.2105/AJPH.91.11.1776

Kelsey, A., Stillinger, D., Pham, T. B., Murphy, J., Firth, S., & Carballar-Lejarazú, R. (2020). Global Governing Bodies: A Pathway for Gene Drive Governance for Vector Mosquito Control. *The American Journal of Tropical Medicine and Hygiene*, *103*(3), 976–985. https://doi.org/10.4269/ajtmh.19-0941

Kofler, N., Collins, J. P., Kuzma, J., Marris, E., Esvelt, K., Nelson, M. P., Newhouse, A., Rothschild, L. J., Vigliotti, V. S., Semenov, M., Jacobsen, R., Dahlman, J. E., Prince, S., Caccone, A., Brown, T., & Schmitz, O. J. (2018). Editing nature: Local roots of global governance. *Science*, *362*(6414), 527–529. https://doi.org/10.1126/science.aat4612

Kolopack, P. A., & Lavery, J. V. (2017). Informed consent in field trials of gene-drive mosquitoes. *Gates Open Research*, *1*, 14. https://doi.org/10.12688/gatesopenres.12771.1

Kyrou, K., Hammond, A. M., Galizi, R., Kranjc, N., Burt, A., Beaghton, A. K., Nolan, T., & Crisanti, A. (2018). A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. *Nature Biotechnology*, *36*(11), 1062–1066. https://doi.org/10.1038/nbt.4245

Long, K. C., Alphey, L., Annas, G. J., Bloss, C. S., Campbell, K. J., Champer, J., Chen, C.-H., Choudhary, A., Church, G. M., Collins, J. P., Cooper, K. L., Delborne, J. A., Edwards, O. R., Emerson, C. I., Esvelt, K., Evans, S. W., Friedman, R. M., Gantz, V. M., Gould, F., … Akbari, O. S. (2020). Core commitments for field trials of gene drive organisms. *Science*, *370*(6523), 1417–1419. https://doi.org/10.1126/science.abd1908

Moloo, Z. (2018, December 19). *Cutting Corners on Consent | by Zahra Moloo*. Project Syndicate. https://www.project-syndicate.org/commentary/target-malaria-gene-drive-experiments-lack-of-consent-by-zahra-moloo-2018-12

National Academies of Sciences, Engineering, and Medicine. (2016). *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK379277/

Neuhaus, C. P. (2018). Community Engagement and Field Trials of Genetically Modified Insects and Animals. *Hastings Center Report*, *48*(1), 25–36. https://doi.org/10.1002/hast.808

Noble, C. et. al. (2016). *Daisy-chain gene drives for the alteration of local populations*. bioRxiv. http://www.biorxiv.org/content/early/2016/06/06/057307

Oliveira, S. de, Villela, D. A. M., Dias, F. B. S., Moreira, L. A., & Freitas, R. M. de. (2017). How does competition among wild type mosquitoes influence the performance of Aedes aegypti and dissemination of Wolbachia pipientis? *PLOS Neglected Tropical Diseases*, *11*(10), e0005947. https://doi.org/10.1371/journal.pntd.0005947

O'Neill, O. (2002). *Autonomy and Trust in Bioethics*. Cambridge University Press. https://doi.org/10.1017/CBO9780511606250

O'Neill, O. (2003). Some limits of informed consent. *Journal of Medical Ethics*, *29*(1), 4–7. https://doi.org/10.1136/jme.29.1.4

O'Neill, O. (2016). *Justice across Boundaries: Whose Obligations?* Cambridge University Press.

Over 160 Organizations Called for Moratorium on Gene Drives at the COP 13. (2016, December 5). Friends of the Earth International. https://www.foei.org/news/friends-earth-international-160-organizations-called-moratorium-gene-drives-cop-13

Peter, F. (2017). Political Legitimacy. In E. N. Zalta (Ed.), *The Stanford Encyclopedia of Philosophy* (Summer 2017). Metaphysics Research Lab, Stanford University. https://plato.stanford.edu/archives/sum2017/entries/legitimacy/

Resnik, D. B. (2014). Ethical issues in field trials of genetically modified disease-resistant mosquitoes. *Developing World Bioethics*, *14*(1), 37–46. https://doi.org/10.1111/dewb.12011

Rittberger, V., & Fischer, M. (2008). *Strategies for Peace: Contributions of International Organizations, States, and Non-State Actors*. Barbara Budrich.

Roberts, A. J., & Thizy, D. (2022). Articulating ethical principles guiding Target Malaria's engagement strategy. *Malaria Journal*, *21*(1), 35. https://doi.org/10.1186/s12936-022-04062-4

Safe Genes. (n.d.). Retrieved January 23, 2019, from https://www.darpa.mil/program/safe-genes

Simoni, A., Hammond, A. M., Beaghton, A. K., Galizi, R., Taxiarchi, C., Kyrou, K., Meacci, D., Gribble, M., Morselli, G., Burt, A., Nolan, T., & Crisanti, A. (2020). A male-biased sex-distorter gene drive for the human malaria vector Anopheles gambiae. *Nature Biotechnology*, 1–7. https://doi.org/10.1038/s41587-020-0508-1

Singh, J. A. (2019). Informed consent and community engagement in open field research: Lessons for gene drive science. *BMC Medical Ethics*, *20*(1), 54. https://doi.org/10.1186/s12910-019-0389-3

Smolenski, J. (2015). CRISPR/Cas9 and Germline Modification: New Difficulties in Obtaining Informed Consent. *The American Journal of Bioethics*, *15*(12), 35–37. https://doi.org/10.1080/15265161.2015.1103816

Smolenski, J. (2019). Gene Drives and Genome Modification in Nonhuman Animals: A Concern for Informed Consent? *Cambridge Quarterly of Healthcare Ethics*, *28*(1), 93–99. https://doi.org/10.1017/S0963180118000427

Synbiowatch. (2016, July 28). *The Case for a Global Moratorium on Genetically-Engineered Gene Drives*. https://www.synbiowatch.org/gene-drives/gene-drives-moratorium/

Texts adopted—COP15 to the Convention on Biological Diversity (Kunming 2020)—Thursday, 16 January 2020. (2020, January 16). European Parliament. https://www.europarl.europa.eu/doceo/document/TA-9-2020-0015_EN.html

Thizy, D., Coche, I., & de Vries, J. (2020). Providing a policy framework for responsible gene drive research: An analysis of the existing governance landscape and priority areas for further research. *Wellcome Open Research*, *5*, 173. https://doi.org/10.12688/wellcomeopenres.16023.1

Thizy, D., Emerson, C., Gibbs, J., Hartley, S., Kapiriri, L., Lavery, J., Lunshof, J., Ramsey, J., Shapiro, J., Singh, J. A., Toe, L. P., Coche, I., & Robinson, B. (2019). Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods. *PLOS Neglected Tropical Diseases*, *13*(4), e0007286. https://doi.org/10.1371/journal.pntd.0007286

Thizy, D., Toe, L. P., Mbogo, C., Matoke-Muhia, D., Alibu, V. P., Barnhill-Dilling, S. K., Chantler, T., Chongwe, G., Delborne, J., Kapiriri, L., Kavuma, E. N., Koloi-Keaikitse, S., Kormos, A., Littler, K., Lwetoijera, D., de Moraes, R. V., Mumba, N., Mutengu, L., Mwichuli, S., … Tountas, K. H. (2021). Proceedings of an expert workshop on community agreement for gene drive research in Africa—Co-organised by KEMRI, PAMCA and Target Malaria [version 2; peer review: 2 approved]. *Gates Open Research*, 15.

WA-IVM Steering Committee Adopts Guidelines for Genetically Based Control of the Malaria Vector | AUDA-NEPAD. (n.d.). Retrieved March 5, 2022, from

https://www.nepad.org/news/wa-ivm-steering-committee-adopts-guidelines-genetically-based-control-of-malaria-vector

Warmbrod, K. L., Montague, M., & Gronvall, G. K. (2022). A Closing Window of Opportunity for Gene Drive Governance in the United States. *Health Security*, *20*(1), 3–5. https://doi.org/10.1089/hs.2022.0009

World Health Organization. (2020). *WHO Position Statement: Evaluation of genetically modified mosquitoes for the control of vector-borne diseases*. WHO.

World Health Organization. (2021). *WHO | The 2021 Updated Guidance Framework for testing genetically modified mosquitoes*.

World malaria report 2021. (2021). https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

Xu, X.-R. S., Bulger, E. A., Gantz, V. M., Klanseck, C., Heimler, S. R., Auradkar, A., Bennett, J. B., Miller, L. A., Leahy, S., Juste, S. S., Buchman, A., Akbari, O. S., Marshall, J. M., & Bier, E. (2020). Active Genetic Neutralizing Elements for Halting or Deleting Gene Drives. *Molecular Cell*. https://doi.org/10.1016/j.molcel.2020.09.003

Thesis Conclusion

The aim of the research, analysis, and synthesis proffered in the works constituting this thesis has been to clarify and offer guidance regarding some murky or contested areas of active debate in deliberations for policy formation and governance of gene drive technologies. Chapter one begins by confronting the most foundational normative question for gene drive technology; is it unethical in principle? After all, if the answer to this question were in the affirmative we could put to rest the whole matter of determining when and under what circumstances its use is appropriate, and just collectively walk away from gene drive technology. However, as has been shown, given epistemically available considerations amenable for public reasoning there is no reason to believe gene drive technology is unethical in principle. In forums of deliberation for public policy formation priority ought to be granted to rational considerations available to all in accordance with the discourse constraints of public reason. It would be irresponsible to grant deliberative weight to considerations which depend on epistemically unjustified axiomatic presuppositions regarding the existence of a normative external frame of reference, such as for religious or ideological considerations. This is particularly true when doing so could result in the avoidable suffering and death of millions of people, as might be the case given the malaria status quo and the declining efficacy of our existing tools for fighting malaria. I hope the reader will find that chapter one of this thesis outlines a clear and rational path for moving beyond exchanges mired in entertaining the possibility that gene drive technology is unethical in principle.

Chapter two contends with the question of whether policy aligned with a prevalent international ethical and regulatory norm, the precautionary principle, would require or support an indefinite global moratorium on the environmental release of any and all engineered gene

drive organisms. I provide a careful analysis of the UNESCO working definition of the precautionary principle; the most relevant iteration given the nature and context of the question, with relation to the use case of gene drive modified mosquitoes for malaria elimination; a leading example of a gene drive application in advanced stages of scientific development and designed for the public good. The conclusion of my analysis is that, at a minimum, the precautionary principle does not align with calls for a global moratorium on all gene drive technology environmental release. And in fact, the values motivating, and substantive content of the precautionary principle appear far more closely aligned with continued research on gene drive modified mosquitoes for malaria elimination, and even field testing and potential eventual deployment under a stepwise and responsible research pathway.

In the article constituting chapter three I aided Target Malaria, a leading non-profit gene drive research consortium aimed at developing and sharing gene drive modified mosquitoes for malaria elimination, to articulate the ethical principles which guide their engagement activities. The paper also provides analytical rationales for selection of the principles, describes how they are aligned with project values, and emerging guidance and best practices within this burgeoning field. Finally, it offers some early lessons learned by Target Malaria over the past several years as they enacted these principles. This contribution is important as it participates in transparency as well as in the iterative creation of best practices for a field that is still in the process of defining these within and for the community of funders, projects, and engagement practitioners associated with area-wide, self-proliferating, environment-targeting, genetically modified organisms for public health ends.

Finally, in chapter four I offer an analysis and argument for identifying the ethically justified locus of deliberative gravity for gene drive modified mosquitoes at the level of political organization constituting a nation-state. I qualify this somewhat by adding that every effort ought to be made to coordinate and find consensus with neighbouring nation-states reasonably predicted to be directly affected by the gene drive intervention in question. However, I do believe in the end that a sovereign state is primarily ethically obligated to do what is in the net best interests of its constituents, so the centre of ethically justified deliberative gravity remains there. This analysis is a significant contribution since there remains a considerable amount of ambiguity and confusion in the existing discourse as to where appropriate jurisdiction for such decisions resides. I am hopeful that this piece goes some way towards pointing future conversations in a constructive, practical, and appropriate direction.

Together these anthologized works represent my first contributions and entrance into the global health ethics academic and policy discourse. The past five years of immersion in this discourse space have been informative, enriching, and intellectually exciting. I hope to merit the opportunity to continue learning and working in this field of scholarship and contributing my time, intellectual curiosity, good faith effort, and skills of analysis and synthesis towards the collective effort of crafting ethical policy and encouraging ethical governance in the sphere of global health, particularly as we integrate novel technologies and methods.

Works Cited for Thesis Intro, Chapter Prefaces, and Conclusion

Adelman, Z., Akbari, O., Bauer, J., Bier, E., Bloss, C., Carter, S. R., Callender, C., Costero-Saint Denis, A., Cowhey, P., Dass, B., & others. (2017). Rules of the road for insect gene drive research and testing. *Nature Biotechnology*, *35*(8), 716–718.

Alphey, L. S., Crisanti, A., Randazzo, F. (Fil), & Akbari, O. S. (2020). Opinion: Standardizing the definition of gene drive. *Proceedings of the National Academy of Sciences*. https://doi.org/10.1073/pnas.2020417117

Bier, E. (2022). Gene drives gaining speed. *Nature Reviews Genetics*, *23*(1), 5–22. https://doi.org/10.1038/s41576-021-00386-0

Esvelt, K. M., Smidler, A. L., Catteruccia, F., & Church, G. M. (2014). Concerning RNA-guided gene drives for the alteration of wild populations. *ELife*, *3*. https://doi.org/10.7554/eLife.03401

National Academies of Sciences, Engineering, and Medicine. (2016). *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK379277/

World Health Organization. (2020). *WHO Position Statement: Evaluation of genetically modified mosquitoes for the control of vector-borne diseases*. WHO.

World malaria report 2021. (2021). https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021