Special issue

What is wrong in extinguishing a species? Charting the Ethical Challenges of using Gene-Drive Technologies to eradicate *A. gambiae* vector populations

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ABSTRACT: This article analyses three ethical arguments against the use of gene-drive technologies to control for, and possibly extinguish, a particular species of vector mosquitoes (Anopheles gambiae) causing the malaria infection. We conclude that none of these arguments is truly persuasive in the specific case and, therefore, that using gene-drive technologies to suppress or eradicate the population of Anopheles gambiae could be ethically justifiable provided certain cautions referring to ecological consequences, evolutionary effects and social engagement of local communities.

KEYWORDS: Gene-Drive; genome-editing; bioethics; CRISPR-Cas9; biodiversity

1. Introduction

In this article we analyze the bioethical implications of using gene-editing and gene-drive technologies to eradicate one species of vector mosquitoes, *Anopheles gambiae*, which is the primary vector of malaria. What follows is divided in four main sections. Section two introduces the burden of mosquito-borne diseases and the need for new vector control strategies. Section three, then, outlines the historical development of biotechnologies for vector controls, from early attempts to exploit selfish genetic elements via breeding programs to recent CRISPR gene-editing techniques. On this basis, section four introduces and discusses three possible arguments according to which extinguishing a species could be considered unethical because: (i) all species have intrinsic and absolute moral value; (ii) species have a moral value that depends on the intrinsic moral value of the individuals belonging to them; (iii) the diversity of species is important as it contributes to the extrinsic value of biodiversity. As we argue, provided certain conditions are met, none of these

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arguments are persuasive in opposing the use of gene-drive technologies to eradicate the *Anopheles gambiae,* a public health intervention that might save millions of human lives over the next years.

2. A steep price to pay: the global burden of mosquito-borne diseases

Due to the SARS-CoV-2 pandemic, a virus that amplified in bats and then transferred to humans through an as yet unidentified intermediate species, the issue of animal-borne diseases (zoonoses) has finally assumed a central role in the scientific and general debate on public health. However, only a relatively small number of species causes significant harms to humans today. Of these, most prominent are those that reduce agricultural output and that cause or transmit diseases.[1] In this respect, the burden of mosquito-borne diseases such as malaria has a prominent role. According to the World Health Organization (WHO), in 2019 over 400.000 persons have died of malaria, the 67% of which were children under the age of five.[2] Furthermore, malaria has other consequences for human health and wellbeing. In 2018 more than 11 million pregnant women have contracted malaria, causing the birth of 900.000 underweight children with higher risks of premature death and developing severe chronic conditions.[3] Of the 24 million of children who contracted the infection in 2018, it has been estimated that nearly 2 million have developed severe or moderate anaemia.[4] Aside from malaria, mosquitoes are also the primary vector of other zoonoses such as the yellow fewer, zika, chikungunya, and dengue.[5] None of these is deadlier than malaria, but their combined effect is estimated to be responsible for 725.000 human deaths a year.[6] It has been supposed that mosquitoes could have been the deadliest animal in human history.[7]

Furthermore, although the memory of the malarial areas in countries such as Italy is still alive, today mosquito-borne diseases disproportionally affect poor and vulnerable populations that already carry a significant burden of socio-economical and health inequalities. In 2018, "85% of global malaria deaths […] were concentrated in 20 countries in the WHO African Region and India; Nigeria accounted for almost 24% of all global malaria deaths, followed by the Democratic Republic of the Congo (11%)".[8] Unsurprisingly, reducing the burden of mosquito-borne diseases has long been

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[1] See A. BURT, *Site-specific selfish genes as tools for the control and genetic engineering of natural populations,* in *Proc. Biol. Soc.,* 270, 1518, 2003, 921-928.

[2] World Health Organization, *World Malaria Report 2019*, https://www.who.int/publications-detail/world-malaria-report-2019 (last visited 28.01.21).

[3] *Ibidem.*

[4] *Ibidem.*

[5] On the current burden of dengue in Africa, see E. MANCINI, R.M. ZAGARELLA, *Modelli deliberativi per l'allocazione delle risorse in sanità: il caso della dengue in Tanzania*, in *Medicina e Morale*, 3, 2019, 313-335.

[6] https://www.who.int/southeastasia/news/opinion-editorials/detail/towards-a-mosquito-free-monsoon (last visited 28.01.21); see also Comitato Etico Fondazione Umberto Veronesi, *Gene-drive e responsabilità ecologica. Parere del Comitato Etico a favore della sperimentazione con popolazioni di zanzare geneticamente modificate,* cit.

[7] https://www.theguardian.com/global/2016/feb/10/should-we-wipe-mosquitoes-off-the-face-of-the-earth (last visited 28.01.21); see also A. ZIELINSKI, *The Ethical Risks of Engineering Mosquitoes into Extinction to Stop Zik*a, in *Think Progress*, 2016, https://thinkprogress.org/the-ethical-risks-of-engineering-mosquitoes-into-extinction-to-stop-zika-88e45e538d25/ (last visited 28.01.21).

[8] World Health Organization, *op. cit.*

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identified as a priority by many institutions and non-governmental organizations committed to reducing global health inequalities.

In general, the efforts to reduce the damages of mosquito-borne diseases have pursued one or more of the following strategies. One is to rely on public-health interventions, from educational programs to enhance health-literacy to the distribution of Insecticide-Treated bed Nets (ITNs). Multiple controlled studies have suggested that ITNs are highly cost-effective in reducing malaria infections and in saving human lives.[9] Despite these encouraging results, however, it is unlikely that this class of interventions may lift the entire burden of mosquito-borne diseases unless it is integrated with other strategies.

A second strategy, then, is to develop effective measures and therapies to prevent or directly treat mosquito-borne diseases. This requires significant investments and years of research. Furthermore, results are not guaranteed: at present there still exists no cure for mosquito-borne diseases such as zika and chikungunya. However, even when effective treatments are available, other factors may prevent or reduce their ability to control or end an epidemic. In this respect, the case of malaria is telling. Today, malaria can be cured if promptly diagnosed and treated.[10] However, in the regions where malaria is endemic diagnostic and treatment options are often lacking or inaccessible, further exacerbating inequalities in access to health. A pilot study is under way to test the first malaria vaccine (RTS,S/AS01, or RTS,S) in three African countries; it will be completed in 2023. In 2014 the RST,S has been tested in a Phase 3 clinical trial that demonstrated that "among children who received four doses, the vaccine prevented approximately 4 in 10 (39%) cases of malaria and 3 in 10 (29%) cases of severe malaria over a four-year period".[11] Due to its relative efficacy, the vaccine is considered a potentially important complementary tool for malaria control efforts rather than a candidate solution for the zoonosis.

Finally, a third strategy is to control for vector populations, mainly insects. Most diseases are transmitted only by a few species of mosquitoes and parasites: in the case of malaria, the main vector is *Anopheles gambiae,* while in the case of dengue, yellow fewer, zika, and chikungunya is *Aedes aegypti.*[12] Reducing or eradicating these vector populations would reduce or eliminate the burden of associated diseases.[13] So far, however, attempts to control vector mosquito populations

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[9] https://www.givewell.org/international/technical/programs/insecticide-treated-nets (last visited 28.01.21).

[10] https://www.who.int/activities/treating-malaria (last visited 28.01.21).

[11] On the ongoing studies for the malaria vaccine see Center for Vaccine Innovation and Access, *The RTS,S malaria vaccine*, https://bit.ly/3rW99ug (last visited 28.01.21).

[12] To be more precise, "Malaria in humans results from infection by any of five species of Plasmodium: P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi. These are transmitted to humans by approximately 50 species of mosquitoes, all belonging to the genus Anopheles. In sub-Saharan Africa, the vast majority of deaths are caused by P. falciparum transmitted by An. gambiae and the closely related An. arabiensis"; J.M. MARSHALL, C.E. TAYLOR, *Malaria Control with Transgenic Mosquitoes*, in *PLoS Med*, 6, 2, e1000020, 0164.

[13] According to the WHO, vector control interventions "have one of the highest returns on investment in public health. Effective vector control programmes that reduce disease can advance human and economic development. Aside from direct health benefits, reductions in vector-borne diseases will enable greater productivity and growth, reduce household poverty, increase equity and women's empowerment, and strengthen health systems". World Health Organization, *Global Vector Control Response 2017-2030,* 2017, 15.

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have achieved mixed results.[14] In part, this has been due to the limited efficacy of traditional methods. Pesticides, for instance, are relatively effective in killing mosquitoes. Yet, over time, mosquitoes tend to evolve forms of pesticide resistance. Furthermore, the use of pesticides has long-term negative impacts on human health and ecosystems[15]. Other traditional methods (i.e. fumigation of affected areas; elimination of breeding habitats, etc.) yield similar results: some are relatively effective, but alone they can hardly be expected to eradicate mosquito-borne diseases[16].

For these reasons, in the last decades, the search for alternative vector control approaches has increasingly turned to the life sciences, and in particular to molecular biology and genetic engineering.

3. Scaling the genomic revolution to ecosystems: the power and promises of gene-drive technologies

The development of biotechnologies to control vector populations has long been in the making. A first turning point has occurred by the mid of the 20th century, when scientists began to study selfish genetic elements able to circumvent the ratios of Mendelian inheritance and force the dynamics of gene frequency change in populations. In 1960 Craig and colleagues proposed a breeding program to favor a biased inheritance of a "male-producing factor" naturally occurring in *Aedes aegypti.*[17] When male mosquitoes carrying this factor breed, the resulting offspring is predominantly male. Thus, by releasing in the environment mosquitoes carrying this selfish element, it is theoretically possible to alter the normal sex-ration and to lower the population of females (the agents of zoonosis) below the frequency required for effective disease transmission. This proposal has been followed by other studies suggesting the use of selfish genetic elements to reduce vector populations, especially in invertebrate populations with short generations, and by the first mathematical model demonstrating how a desirable genetic element may spread to reach *fixation* in a target population.[18] Yet, at the time scientists lacked the molecular tools to engineer desirable genetic elements and associate them to biased mechanisms of genetic inheritance.

Then, after thirty years of research in molecular biology, in 1992 Kidwell and Ribeiro proposed the use of transposable elements (TEs) as a mechanism to drive an engineered gene in a mosquito

[14] On the different strategies currently used to fight malaria see ; see also The National Academies of Science, Engineering, and Medicine, *Gene Drives on the Horizon. Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*, Washington, 2016.

[15] "Synthetic pyrethroids and organophosphates, the two most commonly used sprayed pesticides, have been linked to multiple medical problems, including birth defects, cancer, and chronic dermatologic and respiratory health problems. […]. In addition to individual health risks, there is concern that insecticide spraying may have major unintended environmental impacts, including encouraging mosquito resistance and harming other insect species"; L. GREISMAN, B. KOENIG, M. BARRY, *Control of Mosquito-Borne Illnesses: A Challenge to Public Health Ethics*, in A.C. MASTROIANNI, J. P. KAHN, N.E. KASS. (eds.), *The Oxford Handbook of Public Health Ethics*, https://bit.ly/2RdKJQw, (last visited 28.01.21).

[16] On the limits of traditional approaches for vector control see World Health Organization, *op. cit.*

[17] G.B. CRAIG, W.A. HICKEY, R.C. VANDEHEY, *An inherited male-producing factor in Aedes aegypti*, in *Science*, 132, 3443, 1887-1889.

[18] The National Academies of Science, Engineering, and Medicine, *op. cit.*

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population.[19] TEs are a special kind of selfish genetic element "able to spread quickly through a population due to their ability to replicate within a host genome and hence to be inherited more frequently in the offspring's genome".[20] Today we know that TEs are a fundamental source of genetic variation and have a prominent role in favoring genome plasticity. They not only produce deleterious mutations, but can promote the adaptability of species. For example, the genome of invasive species, including mosquitoes such as *Aedes albopictus*, are rich in TEs. Despite the initial excitement about TEs, the first studies evidenced some of their structural limitations, such as their low activity in vector mosquitoes, low replication rate, and vulnerability to losing internal sequences during replication.[21] To solve these issues, in 2003 Burt suggested the use of the homing endonuclease gene (HE), a site-specific selfish gene, to drive a specific genetic element in a population. HE was then at the centre of researches as possible basis for targeted gene therapy – an experimental approach in its early infancy. Burt proposed to extend these lines of research to vector control, arguing that HE had several advantages over previous candidates (such as TEs) due to its evolutionary stability, reversibility and applicability.[22]

These pioneering studies opened a new phase of research into so-called "gene-drives". In general, a gene drive can be defined as "a system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced".[23] Under traditional Mendelian inheritance, the offspring has a 50% chance of inheriting a genetic element from a parent organism. Gene-drives are molecular accelerators that alter this ratio by inducing the preferential increase of a specific *genotype* – and, thus of the associated *phenotype* – "from one generation to the next, and potentially throughout the populations".[24] Also, these studies had the merit of calling for an open and public discussion over *the ethics* of gene-drives, and in particular "on the desirability of eradicating or genetically modifying particular species".[25]

These concerns acquired a new sense of urgency with the discovery of CRISPR (Clustered regularly-interspaced short palindromic repeats). CRISPR are segments of bacterial DNA that in conjunction with the guide protein Cas9 allow the editing of the genome of potentially any living organism. Gene-editing techniques based on CRISPR, in fact, allow for the insertion, deletion, copy and paste, or replacement of specific genes in a way that is sometimes orders of magnitude more precise, cheaper and simpler than previous techniques. Indeed, CRISPR gene-editing biotechnologies represent one of the major breakthroughs in the history of the life sciences due to their endless implications, in and

[19] Cfr. M.G. KIDWELL, J.M. RIBEIRO, *Can transposable elements be used to drive disease refractoriness genes into vector populations?*, In *Parasitology*. *Today*, 8, 10, 1992, 325-329.
[20] J.M. MARSHALL, C.E. TAYLOR, *op. cit*., 0165.
[21] A. BURT, *Site-specific selfish genes as tools for the control and genetic engineering of natural populations*, in *Proceedings Biological Science*, 270, 1518, 2003, 921-928.
[22] A. BURT, *op. cit.,* 922-23.
[23] The National Academies of Science, Engineering, and Medicine, *op. cit.*, 21.
[24] *Ibidem*.
[25] A. BURT, *op. cit,* 921.

beyond biology and biomedicine.[26] Being a more accessible technique, of course it also poses greater control problems.

Among their huge and multiple applications, CRISPR-based technologies provided a new and powerful method of engineering gene-drives as well. In 2015, different research groups were able to show that it was possible to use CRISPR to create specific gene-drives in yeast, fruit-flies and – most importantly – in vector mosquitoes.[27] Thus, only three years after its first demonstration as a gene-editing tools, CRISPR, paired with advanced knowledge about selfish genetic elements, "enabled a breakthrough in what scientists had been studying for more than 50 years".[28]

These studies also opened the possibility of creating different gene-drives to achieve diverse purposes. With respect to the use of gene-drives to control vector populations, two main approaches have been conceived. The first one aims at *population suppression*, that is, at spreading a genetic element that causes the number of individuals in a population to decrease, potentially driving it to extinction.[29] The second approach, instead, aims at *population replacement*, that is, at spreading a genetic element in a population that causes a population's genotype to change its frequency (e.g. spreading a gene that makes mosquitoes non-infectible by, or unable to transmit, dangerous pathogens such as *Plasmodium falciparum* causing malaria).[30]

Furthermore, these first studies have been crucial in highlighting and then overcoming various technical hurdles. One of the most pressing technical issue in the development of gene-drives for vector control is the emergence of counter-mutations that might reduce over time the driver capacity, producing resistance.[31] In this respect, an important step has been taken in a study in 2018 by Kirou et al. in which scientists used CRISPR to create a gene-drive targeting the *doublsex gene* (dsx).[32] This gene is crucial to ensure the reproduction of the species, it is strongly conserved by natural selection and therefore highly resistant to mutations. The studies have demonstrated that

[26] On the implications of gene-editing techniques for biomedicine, see Comitato Etico Fondazione Umberto Veronesi, *L'editing del genoma umano tra etica e democrazia*, in *The Future of Science and Ethics*, 3, 2018, 52-61.

[27] On the first studies to create gene-drives in mosquitoes with CRISPR see V.M., GANTZ, N. JASINSKIENE, O. TATARENKOVA, A. FAZEKAS, V.M. MACIAS, E. BIER, A.A. JAMES, *Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito* Anopheles stephensi, in *Proc. Natl. Acad. Sci.*, 112/E6736-E6743, 2015; and A. HAMMOND, R. GALIZI, K. KYROU, A. SIMONI, C. SINISCALCHI, D. KATSANOS, M. GRIBBLE, D. BAKER, E. MAROIS, S. RUSSELL, A. BURT, N. WINDBICHLER, A. CRISANTI, T. NOLAN, *A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector* Anopheles gambiae, in *Nat. Biotechnol.*, 34, 1, 2016, 78-83.

[28] The National Academies of Science, Engineering, and Medicine, *op. cit.,* 13.

[29] *Ivi*, 16.

[30] Furthermore, it is also important to distinguish between *self-propagating* and *self-limiting gene-drives*; on this aspect see J. STEPHANIE JAMES, F.H. COLLINS, P.A. WELKHOFF, C. EMERSON, H. CHARLES, J. GODFRAY 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*, in *Am. J. Trop. Med. Hyg.*, 98, 6, 2018, 1-49.

[31] On the technical difficulties of the first attempts to engineer robot gene-drives in mosquitoes see E CALLAWAY, *Gene drives thwarted by emergence of resistant organisms*, in *Nature*, 542, 7639, 2017.

[32] K. KYROU, A.M. HAMMOND, R. GALIZI, N. KRANJC, A. BURT, A.K. BEAGHTON, T. NOLAN, A. CRISANTI, *A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged* Anopheles gambiae *mosquitoes*, in *Nature Biotechnology*, 36, 2018, 1062-1066.

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the mutations created with CRISPR on *dsx* produced healthy males but sterile females in *Anopheles*. In just eleven generations the mutation has spread to the 100% of the individuals, leading to complete population collapse.[33] The speed of action is inversely proportional to the probability of developing resistance. Normally, starting from 600 mosquitoes after 11 generations, 20 million individuals are obtained; with the gene-drive on *dsx*, instead, after 11 generations the result was 0.[34] Furthermore, the resistant variants that have arisen in each generation have not blocked the spread of the driver. For this reason, the suppression gene-drive, whose killing action is faster, protects more from the risk of resistance. Following these successes, other researchers have begun to consolidate these results and planned the first experiments in controlled environments. Today, multiple gene-drive technologies based on CRISPR-Cas-9 and other genome-editing techniques have already been tested in controlled experiments. Some of these interventions will presumably soon be released in the environment, precipitating a host of pressing legal, political, regulatory, and ethical questions.

4. Three ethical arguments to object the use of gene-drives to eradicate Anopheles gambiae

CRISPR gene-editing biotechnologies coupled with gene-drive mechanisms provide powerful tools to control or suppress vector populations. However, the prospect of eradicating entire populations, varieties and species through these technologies is morally problematic and attracted a number of criticisms.[35] Although the development of gene-drives biotechnologies raises a host of complex ethical issues, in this section we limit our analysis to the potential moral objections of using gene-drive biotechnologies to extinguish one species of mosquitoes: *Anopheles gambiae*. More precisely, in this section we explore three possible ethical arguments against the eradication of *Anopheles*, arguing that they all fail to provide a convincing rationale to oppose this intervention.

4.1 First Argument: species have intrinsic and absolute moral value

According to Pugh, a first way to argue against the use of gene-drive technologies is to contend that each species has intrinsic and absolute moral value.[36] To exemplify this position, Pugh cites the entomologist R.L Metcalf, who, in objecting to the eradication of species as a method for pest control, noted that "species should be regarded as sacred and man indeed has no right to destroy them".[37] Pugh then also quotes M. Challenger – author of the best-selling book *On Extinction: How*

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[33] *Ibidem*.

[34] *Ibidem*.

[35] For an overview of ethical challenges of gene-drives technologies see The National Academies of Science, Engineering, and Medicine, *op. cit.;* Comitato Etico Fondazione Umberto Veronesi, *Gene-drive e responsabilità ecologica. Parere del Comitato Etico a favore della sperimentazione con popolazioni di zanzare geneticamente modificate, cit.*; J. STEPHANIE JAMES, F.H. COLLINS, P.A. WELKHOFF, C. EMERSON, H. CHARLES, J. GODFRAY et al.*, op. cit.*

[36] See J. PUGH, *Driven to extinction? The ethics of eradicating mosquitoes with gene-drive technologies*, in *Journal of Medical ethics*, 42, i9, 2016, 578-581.

[37] See J. PERKINS, *The Philosophical Foundations*, in J. PERKINS (ed), *Insects, Experts, and the Insecticide Crisis: The Quest for New Pest Management,* 2012, 183-207; cited in J. PUGH, *op. cit.*

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we became estranged from nature –, who observed (adopting the standard argument of the "slippery slope") that "I do think there's something more robust: the sanctity of life. If you start getting cavalier about the existence of a living being, if we start to think it's OK to eradicate something because it's a threat to us, we put other ideas about the sanctity of life in question".[38] Following a common categorization in bioethics, Pugh classifies both quotes under the category of the "sanctity of life" arguments against gene-drives. This label, however, is misleading. As shown by Jones, and contrary to a popular belief, the "sanctity of life" view is not tied to any religious tradition; it emerged in bioethics only in 1970s as a way of constructing a caricature of deontological positions over the permissibility of abortion and euthanasia.[39] Nevertheless, for the sake of the argument, let us depart from Pugh's reading as a way to introduce what we may label as the "expanded sanctity of life view". According to the general version of this view, extinguishing a species is always wrong, for *all biological life* has intrinsic and absolute moral worth, regardless of the species in question. Obviously, such a view is absurd. To hold that "all life forms have intrinsic and absolute moral value", in fact, would amount to hold a view that is factually incompatible with one's own life. We constantly kill other living organisms for our ends. The death of individuals and species by other individuals and species is at the basis of every ecological network and the evolution of every ecosystem. Of course, we are dramatically accelerating the extinction of other species, to the point that today we talk about the Sixth Mass Extinction of biodiversity, but this is not causally correlated with the planned and ethically motivated extinction of a single population or species of insects (see 4.3). We use plants for food and many other vital activities, and we kill bacteria with antibiotics.[40] Understood in this generalized way, the expanded view is "hopelessly inconsistent with everyday life". Hence, it must be rejected.

A more limited (and sensible) version of this view is to hold that only *species*, rather than all life forms have intrinsic and infinite moral value. According to this view, what is "sacred" is not life in general or individual organisms, but rather *species* in themselves.[41] On this view, killing one or more

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[38] See https://www.theguardian.com/global/2016/feb/10/should-we-wipe-mosquitoes-off-the-face-of-the-earth (last visited 28.01.21); cited in J. PUGH, *op. cit.*

[39] D.A. JONES, *An unholy mess: why 'the sanctity of life principle' should be jettisoned*, in *The New Bioethics*, 22/3, 2016, 185-201. The tile of Jones's article is already explicit; in it he concludes: "The language of 'sanctity', in relation to the ethics of killing, emerged in a modern context to encourage in legal, ethical and theological discussion a false dichotomy between a supposedly religiously-based taboo (sanctity of life) and the making of prudential decisions about life sustaining treatment (quality of life). [T]o lend support that the phrase 'sanctity of life' serves only to perpetuate a discourse that is both confused and dangerous […]. Given that mistaken or contradictory conceptions of 'the sanctity of life' are ubiquitous, it is better to recognise that this is an unhelpful place to start"; see D.A. JONES, *op. cit.*

[40] See J. PUGH, *op. cit*. As P. Singer noted "People often say that life is sacred. They almost never mean what they say. They do not mean, as their words seem to imply, that life itself is sacred. If they did, killing a pig or pulling up a cabbage would be as abhorrent to them as the murder of a human being. When people say that life is sacred, it is human life they have in mind"; P. SINGER, *Practical ethics*, 1993, Cambridge, 83.

[41] Pugh suggests that it is in this sense that one should read Metcalf's remark that we must regard species *as if they were sacred.* A more sensible reading of this quote, however, is that it is not concerned with *moral value*, but with *respect* and r*everence*. On this aspect, Jones noted "Similarly the traditional prohibition on medical homicide does not imply that greater length of life is always the highest value, to be achieved at any cost and by any means. It is, rather, the claim that it is contrary to medical ethics intentionally to end the life of an

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mosquitoes in our backyard could be morally permissible, while extinguishing *Anopheles gambiae* as a whole species would be not. Yet, also this view faces insurmountable theoretical issues. First, it is premised on the idea that a species can possess moral status as a collective entity regardless of the moral status of the individuals that belong to it. But the claim that "moral status" is an emergent property in the case of species is not self-evident and requires further explanation[42]. Second, and more importantly, the claim that all species are "sacred" – i.e. possess intrinsic and absolute moral value – is problematic for it entails that a species of bacteria, yeasts, mosquitoes or plants has *the same moral value* as *Homo sapiens*. Hence, to hold that all species have "intrinsic and absolute moral worth" entails that humanity has the same moral value as a species of yeasts, or plants. This is, at best, a highly counterintuitive conclusion, and which imply the somewhat controversial possibility that human beings can renounce any privileged point of view about themselves and their own evolutionary interests (the same paradox of those who would like to attribute rights, *human* rights, to plants and bacteria). In fact, sometimes eradicating another species may represent a desirable and justifiable aim. Consider, for instance, the case of the eradication of smallpox. Smallpox is fatal in nearly 30% of the cases and it has been estimated that it has killed 300 millions of human beings in the twentieth century alone. Smallpox was finally eradicated in 1980 following extensive vaccination campaigns. In this case, it is undeniable that eradicating the *Variola major* and *Variola minor* – the species of viruses causing smallpox – has been not only one of the greatest accomplishments of contemporary medicine but also a desirable and ethically justifiable outcome. Yet, if the adherent of the expanded sanctity of life view is understood to claim that "all living species are sacred", "then this vaccination programme would have amounted to a morally abhorrent form of 'speciecide'".[43] Again, a conclusion that would sound grossly exaggerated and counterintuitive to most.

Therefore, it seems that even under this second more charitable reading the expanded view of the sanctity of life is ultimately untenable. One cannot convincingly object to the use of gene-drive technologies to eradicate *Anopheles gambiae* on the grounds that either "all life" or "all species" are sacred – if by "sacred" one means that they possess *intrinsic* and *infinite* or absolute moral value. The consequence would be to make human life impossible, or to fall into the illusion of being able to renounce any form of anthropocentrism.

4.2 Second argument: the moral value of species depends on the moral value of their individual components

A second argument, then, is to contend that extinguishing a species may be morally wrong not because species have intrinsic moral value, but because *individuals* belonging to them have intrinsic moral value (or status). On this view, extinguishing *Homo sapiens* would be wrong simply because it would be wrong to kill billions of human beings who have moral value, and conversely, killing a single

innocent human being. Rather than the inviolability of life being an account of the value of length of life, it is simply a recognition of the disrespect that is shown to life when it deliberately destroyed"; see D.A. JONES, *op. cit.*

[42] Scholars like Russow, for instance, have provided convincing arguments to oppose the view that "obligations to a species might arise out of certain putative rights or interests of a species"; cfr J. PUGH, *op. cit.*

[43] J. PUGH, *op. cit.*

human being is like killing humanity itself. Peter Singer, in his classic *Practical Ethics*, defends a similar position as he criticizes the view of deep ecologists such as Bill Devall and George Session who attribute intrinsic and infinite moral value to entities such as *ecosystems* and *species*. As Singer concluded, it is better to "confine ourselves to arguments based on the interests of sentient creatures, present and future, human and non-human", for arguments centred on "holistic entities" are either metaphorical or fall into the same objections of the positions based on the sanctity/reverence of life.[44] Following these remarks, in this section we discuss some implications of Singer's utilitarian view in relation to the ethics of eradicating the species *Anopheles* via gene-drive technologies.

First of all, according to Singer, only *sentient* non-human animals have moral value, as they are the only creatures capable of having "morally relevant interests". More precisely, on Singer's view, non-human animals possess morally relevant interests only if they possess, at least, the minimal capacities "to suffer or experience enjoyment or happiness". Indeed, humans – as well as other primates, pigs, birds, or fishes – normally possess such capacities; therefore, they all have "morally relevant interests" in not being harmed or killed. In other cases, however, the issue of whether non-human animals possess or lack the minimal capacities to be sentient, and therefore to have morally relevant interests, is less clear-cut. In this paper, we focus our bioethical analysis only on invertebrates, namely mosquitos, and not on vertebrates and mammals such as invasive rodents, for which eradication interventions from islands (i.e. Floreana, Galápagos)[45] are being planned. Thus, our question is targeted: do insects and mosquitoes have some degree of morally relevant interests in Singer's minimal sense? Here there are two possibilities. One is that mosquitoes are not sentient, and therefore they do not have *any* moral status. In this case, one could simply not rely on this argument to object to the use of gene-drive technologies to eradicate *Anopheles.* The other possibility is that mosquitoes have some of these minimal capacities, and therefore killing them would be *prima facie* wrong, as it would be to eradicate one of their species. Which of these alternatives is correct?

Answering this question is less straightforward than it might appear at first. Specifying and assessing the criteria for which non-human animals possess or lacks moral status is, in fact, a notoriously controversial task.[46] Furthermore, there exists an ongoing debate in entomology over whether, and

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[44] "There is, of course, a real philosophical question about whether a species or an ecosystem can be considered as the sort of individual that can have interests, or a 'self' to be realised […] For it is necessary, not merely that trees, species, and ecosystems can properly be said to have interests, but that they have morally significant interests. If they are to be regarded as 'selves' it will need to be shown that the survival or realisation of that kind of self has moral value, independently of the value it has because of its importance in sustaining conscious life […], In this respect trees, ecosystems, and species are more like rocks than they are like sentient beings; so the divide between sentient and non-sentient creatures is to that extent a firmer basis for a morally important boundary than the divide between living and non- living things, or between holistic entities and any other entities that we might not regard as holistic"; P. SINGER, *op. cit*, 82-83.

[45] K.J. CAMPBELL, J.R. SAAH , P.R. BROWN , J. GODWIN , F. GOULD et al., *A potential new tool for the toolbox: assessing gene drives for eradicating invasive rodent populations*, in C.R. VEITCH, M.N. CLOUT, A.R. MARTIN, J.C. RUSSELL AND C.J. WEST (eds.), *Island invasives: scaling up to meet the challenge*, 2019, 6-14.

[46] Today there exists a plurality of accounts identifying a wide range of capacities and properties that might provide the basis to attribute "moral status" or "standing" to non-human animals – such as sentience,

to what extent, non-human animals like mosquitoes, fruit flies and similarly complex organisms have or not the minimal capacities to feel pain, suffer, and in general to experience and process nociceptive stimuli.[47] Interestingly, for our present purpose, we can largely remain agnostic over these intricate issues. The reason is that gene-drive technologies operate in a fundamentally different way than other vector control strategies like pesticides. To see how this aspect makes a practical difference in the context of the present analysis, let us assume, for the sake of the argument, that mosquitoes have some minimal moral interests. This would entail, at least, that mosquitoes have the capacities to experience pain and suffering and therefore an interest in not being harmed or killed.

Interestingly, even if this were the case, a utilitarian adopting Singer's view would still lack a convincing rationale to oppose the use of most gene-drive technologies to eradicate the *Anopheles*. Gene-drive interventions, in fact, do not necessarily cause mosquitoes to experience suffering or die prematurely.[48] Rather, a species that has been genetically modified to spread a gene-drive like the one tested by Kirou et al. (2018) – which skews the sex-ratio by causing all female mosquitoes to be sterile – would simply be phased out over time. If these techniques were implemented successfully, "individual mosquitoes would live and die in the same way that they would have done in the absence of the intervention; they will just fail to reproduce", without being aware of it.[49] Therefore, even if we assume that mosquitoes have minimal moral interests, this would still not provide a convincing reason to object to the use of gene-drive technologies for population suppression – at least, from the point of view of Singer's utilitarian view.[50] Unless we think mosquitoes can suffer from being sterilized, which seems frankly absurd.

Moreover, adopting Singer's view would lead to a second, and decisive, series of considerations in favor of gene-drive interventions. Singer is one of the most influential proponents and advocates of the principle of the "equal consideration of interests" and, consequently, of *anti-speciesism.*[51] According to this principle, one should equally consider all affected interests when calculating the

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rationality, moral agency, dignity, and/or the capacities to feel pain, pleasure and emotions; for an overview see L. GRUEN, *The Moral Status of Animals*, in E.N. ZALTA (ed.), *The Stanford Encyclopedia of Philosophy,* (Fall 2017 Edition), https://plato.stanford.edu/archives/fall2017/entries/moral-animal (last visited 28.01.21).

[47] See, for instance, M.K. THANG, Q. WANG, J. MANION, L.J. OYSTON, M. LAU et al., *Nerve injury drives a heightened state of vigilance and neuropathic sensitization in Drosophila,* in *Science Advances*, 5, 7, 2019, eaaw4099.

[48] There are, however, notable exceptions. For instance, in 2021 750 millions of transgenic mosquitoes will be released in Floria in an effort to reduce the vector populations of Zika. These transgenic mosquitoes have been created by a US operated company Oxitec. The specific genetic modification developed by Oxitec, however, does reduce the lifespan of male mosquitoes; see D.O CARVALHO, A.R. MCKEMEY, L. GARZIERA, R. LACROIX, C.A. DONNELLY, L. ALPHEY et al., *Suppression of a Field Population of Aedes aegypti in Brazil by Sustained Release of Transgenic Male Mosquitoes*, in *PLoS Neglected Tropical Diseases*, 9, 7, 2015, e0003864.

[49] J. PUGH, *op. cit.*

[50] It can, however, provides a good argument to chose one gene-drive intervention over others. In fact, other things beings equal, recognizing that mosquitoes have morally relevant interests would provide a powerful argument in favor of developing gene-drive technologies aimed at replacing their population rather than suppressing it.

[51] According to Singer, one should equally consider all affected interests when calculating the rightness of an action – regardless of other factors such as the sex or *species* of the subjects in question; see P. SINGER, *op. cit*, ch. 1-2.

rightness or wrongness of an action, regardless of other factors such as one's skin colour, sex, or *species*. Endorsing this principle, however, does not entail that all interests are equal, but only that they ought to be equally considered. "When we come to consider the value of life – Singer writes –, we cannot say quite so confidently that a life is a life, and equally valuable, whether it is a human life or an animal life. It would not be speciesist to hold that the life of a self-aware being, capable of abstract thought, of planning for the future, of complex acts of communication, and so on, is more valuable than the life of a being without these capacities".[52] One can thus be antispeciesist and recognizes that, other things being equal, the moral interests of humans weigh far more than those attributable to non-human animals lacking complex cognitive capacities, such as mosquitoes.

With respect to the ethics of gene-drive technologies, this implies that, in any case, the interests that might be attributed to *Anopheles* ought to be weighed against the interests of millions of human beings that will suffer and die, and be worse off in case effective gene-drive technologies are withhold. While it is difficult to provide an exact estimation in such cases, with respect to vector control for malaria is hard not to conclude that the moral interests – i.e. the capacity to suffer, think, plan for the future, and flourish over time – of humans are almost incommensurable with respect to those of mosquitoes whose lifespan is of maximum two weeks. Given the significant burden of disease of malaria, and the difference between the moral interests of human and mosquitoes, other things being equal, if we adopt Singer's utilitarian view the eradication of *Anopheles* appears not only *justifiable*, but also *desirable* and ethically motivated. If anything, the results of such utilitarian calculations would provide a compelling ethical rationale to develop and release gene-edited mosquitoes (together with all other preventive actions/interventions against health inequalities) and save human lives.

Thus, also this second utilitarian argument fails to provide a persuasive basis to argue against the eradication of *Anopheles* via gene-drive technologies. Even if one grants to mosquitoes some kind of minimally relevant moral interests – a claim that is very dubious –, given the principle of the equal consideration of interests one would still retain good reasons to promote, rather than withhold, the use of such biotechnologies.

A possible objection to this conclusion is that it is premised on the view that what matters are only the interests of presently living mosquitoes. What about the interests of the beings that will never be born because of the gene-drive technologies? This objection introduces a variant of the second argument for which species have a moral status that depends both on the moral status of presently and future living organisms belonging to them. This line of reasoning leads to intricate moral issues, which, again, we can fortunately sidestep in analyzing the ethics of gene-drive technologies for the case at hand given the incommensurable different weights between the moral interests of present and future humans and the presumed moral interests of present and future mosquitoes. Comparatively, from a utilitarian and pragmatic point of view, this problem would have been much more pressing if the non-human animals in question were clearly sentient (e.g. primates) and the number of human lives saved and/or of human suffering spared would have been not as significant as in the case of malaria.

[52] *Ivi*, 61.

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4.3 Third argument: the diversity of species contributes to the extrinsic value of biodiversity

A third and possible argument against the use of gene-drive technologies to eradicate *Anopheles,* then, is that the diversity of the species contributes to the extrinsic value of *biodiversity*. Today, preserving biodiversity is considered an important value in environmental ethics as well as in biolaw. In general, the term "biodiversity" refers to the variety of all lifeforms.[53] Biodiversity may be defined in different ways, from molecular to ecological levels, but it is commonly understood as encompassing at least three dimensions: the diversity between all species, the genetic diversity within each species, and the diversity within and between ecosystems.[54] Currently, biodiversity is under lethal threat. Because of human actions (deforestation, invasive species, demographic growth, pollutions, over-hunting and over-fishing, climate change), species have been disappearing at 50-100 times the natural rate, and this loss is predicted to rise dramatically.[55] The loss of biodiversity provides an additional reason to evaluate with caution any intervention aimed at extinguishing a species. If we agree that to extinguish other lifeforms is unethical as it compromises biodiversity, then we would have a legitimate objection to the use of gene-drive technologies to suppress *any* species, including *Anopheles*.

On this basis, in this section we discuss a specific argument for which reducing biodiversity is morally wrong as it may jeopardize the survival and wellbeing of humanity, which depend on biodiversity and ecosystem services. The idea that biodiversity – and nature in general – must be preserved primarily for the sake of humanity is, of course, not new.[56] The 1992 *Convention on Biological Diversity*, for instance, affirms that all contracting parties recognize the "intrinsic value of biological diversity and of the ecological, genetic, social, economic, scientific, educational, cultural, recreational and aesthetic values of biological diversity and its components".[57] This passage seems to attribute both an intrinsic as well as an extrinsic value to biodiversity. However, in this section we shall limit our discussion only to the latter aspect.[58] As the Secretariat of the Convention explains in another document, "[p]rotecting biodiversity is in our self-interest. Biological resources are the pillars upon

[53] For an overview of the history of the term "biodiversity", and of the conceptual issues arising from the various attempts at defying it in contemporary philosophy of biology and environmental ethics see D. FAITH, *"Biodiversity"*, in E.N. ZALTA (ed.), *The Stanford Encyclopedia of Philosophy* (Fall 2019 Edition), https://stanford.io/39NWALw , (last visited 28.01.21).

[54] Cfr. Secretariat of the Convention on Biological Diversity, *How the Convention on Biological Diversity promotes nature and human well-being*, 2000, https://www.cbd.int/convention/guide/?id=web (last visited 28.01.21).

[55] *Ibidem*. See also: T. PIEVANI, *Earth's Sixth Mass-Extinction Event*, in *Science Direct*, Elsevier – Online Reference Database: Earth Systems and Environmental Sciences, online 9, 2015, doi 10.1016/B978-0-12-409548-9.09216-2.

[56] See P. SINGER, *op. cit*, 265-268.

[57] United Nations, *Convention on Biological Diversity,* 1992 https://www.cbd.int/doc/legal/cbd-en.pdf (last visited 28.01.21). The *Convention* was opened for signature at the United Nations Conference on Environment and Development in Rio de Janeiro in June 1992 and has as today has been ratified by over 150 countries, providing and important reference for international laws over ecological matters.

[58] It is also worth noting that specifying in which sense "biodiversity" could or should be considered something intrinsically valuable from a moral point of view is not an easy task. On this issue, see, for example, D. FAITH, *op. cit*.

which we build civilizations. Nature's products support […] diverse industries [….]. The loss of biodiversity threatens our food supplies, opportunities for recreation and tourism, and sources of wood, medicines and energy". Because of the instrumental value of biodiversity, this document concludes that it is "unethical to drive other forms of life to extinction, and thereby deprive present and future generations of options for their survival and development". With respect to the ethics of gene-drive technologies, the relevant question to ask is, therefore, what impact the eradication of *Anopheles* could have on biodiversity and for present and future generations.

In answering this question two considerations are in order. First, from the point of view of the diversity between species, if these interventions were successful, then one species of mosquitoes – the *Anopheles* – would likely cease to exist. However, it should be noted that there are more than 3500 known species of mosquitoes, the *Anopheles* being just one of them. Eradicating the *Anopheles*, then, would not be tantamount to extinguish *all* mosquitoes, but only *one* of their many species. Moreover, according to ecological and evolutionary principles, the use of gene-drive technologies may also favor other species of non-zoonotic mosquitoes and insects living in the same areas – e.g., by reducing the current use of insecticides as anti-malaria strategies and/or by freeing new ecological niches.

Second, assessing the wider implications of an intervention that takes place at the level of an entire species and ecosystem is a complex and difficult task. Indeed, "[r]eleasing gene drives into the environment means that complex molecular systems will be introduced into complex ecological systems, setting off a cascade of eco-evolutionary dynamics. Key considerations include fitness, species dispersal, gene flow, ecosystem dynamics, and evolution"[59]. What kind of effect should be expected on the ecosystem if we decide to release gene-edited *Anopheles* mosquitoes?

In the last years, a plethora of rigorous empirical studies have been conducted with the aim of answering this kind of questions and estimating the environmental implications of extinguishing *Anopheles g.* species. Significantly, a recent and comprehensive review of the existing literature 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".[60]

Thus, according to available empirical evidence, it seems that the impacts of eradicating *Anopheles* on biodiversity is likely to be very low, for no other insectivorous species is entirely dependent on

[59] The National Academies of Science, Engineering, and Medicine, *op. cit*., 34.

[60] C.M. Collins, J.A. Bonds, M.M. Quinlan, J.D. Mumford, *Effects of the removal or reduction in density of the malaria mosquito, Anopheles gambiae s.l., on interacting predators and competitors in local ecosystems*, in *Medical and Veterinary Entomology*, 33, 2019, 10.

them for its own survival. Prudentially, considering the complexity of ecological systems, this prediction will have to be carefully verified first in controlled environments, and then through controlled release phases in localized environments, with stringent step-by-step controls. On the other hand, it is clear that the eradication of *Anopheles gambiae* could have a tremendous positive impact on present and future generation by reducing or eliminating the various health and economic burdens of malaria. In fact, we know that the poverty of the populations living in the areas with the highest biodiversity is itself a threat to biodiversity, which is seen as a subsistence resource for those who have nothing to make a living. Other things being equal, then, if the primary value to be considered is the good of present and future generations, then the burden of proof should arguably fall those willing to resist the use of gene-drive interventions rather than on those proposing their adoption.

5. Conclusions and additional cautions

Given the burden of mosquito-borne zoonoses – and especially of malaria – in this article we have argued that the use of gene-editing techniques to create gene-drives finalized at suppressing *Anopheles g.* population is, at least, *prima facie* ethically permissible. In particular, we have showed that the use of such interventions cannot be convincingly objected from the point of three possible arguments based, respectively, on the claim that: (i) all life or all species have intrinsic and absolute moral value; (ii) extinguishing a species is necessarily wrong if the individuals comprising it have some degree of morally relevant interests; and (iii) extinguishing a species is ethically wrong as it jeopardizes biodiversity and thus the present and future of humanity. If this is the case, the gene drive techniques with the purpose of replacement and not of suppression (so, without extinction) seem even more ethically admissible, with the release of mosquitos genetically modified in order to no longer be carriers of malaria (though, given the technical risk of resistance to be controlled).

However, it should be emphasized that our perspective in favor of the use of gene-drives to eradicate *Anopheles* should be assessed by taking into account at least three considerations. First, that the validity of our conclusions apply only insofar as these technologies are used to eradicate population of vector mosquitoes carrying severe and fatal diseases. If the same techniques were be used to create gene-drives in other species, for example in agriculture or for vertebrate species such as invasive rodents, then the same arguments would lead to different conclusions. For instance, if instead of the eradication of *Anopheles* the same biotechnologies would be used to create a gene-drive in a sentient mammal species, then both the second and the third argument would need to be re-evaluated, as such a species might have significantly different moral interests as well as a different impact on biodiversity and thereby on human survival and flourishing.

Second, gene-drive is a biotechnology able of generating hereditary effects and therefore has evolutionary implications. Although reverse gene-drives are being studied, such interventions are irreversible so far. Another reason for caution is that gene-drives producing homozygosis during meiosis and accelerating changes in gene frequencies until fixation tend to reduce genetic variability in natural populations, a precious asset that we should alter only with adequate arguments. Therefore, an ethic of responsibility is necessary for gene-drive applications.[61]

Third, even in the specific case of assessing the ethical impact of vector control strategies, the use of gene-drive technologies raises many other issues that ought to be properly addressed. These include, among many other important concerns, issues such as: the ethics of carrying out responsible experimentations in confined and controlled environments, in order to test the techniques for unintended consequences in the targeted environments; the ethics of respecting current International norms in scientific research about biosecurity and responsible innovation; the proper engagement of the local populations that live in areas in which the gene-edited mosquitoes will be released, as well as of other potential stakeholders.[62] We need a democratic alliance between advanced science and biotechnologies, environmental protection, and local communities. We should always consider these promising and powerful biotechnologies a common good at the service of communities, well-being and peace. They must certainly not be intended as an alibi for not intervening also on the social and economic aspects that favor the spread and permanence of devastating zoonoses such as malaria. As we have explained elsewhere, the use of new and powerful biotechnologies requires not only ethical awareness, but also a comprehensive effort that ought to consider many other social, economic and ecological aspects.[63]

[61] C. Emerson, S. James, K. Littler, F. Randazzo, *Principles for gene drive research*, in *Science*, 358, 2017, 1135-1136.

[62] On the various technical and ethical challenges of experimenting on gene-drive in mosquitoes population see J. Stephanie James, F.H. Collins, P.A. Welkhoff, C. Emerson, H. Charles, J. Godfray et al., *op. cit.*; on the broader ethical and social challenges of these biotechnologies beyond the experimental phase see, instead, The National Academies of Science, Engineering, and Medicine, *op. cit.*

[63] Comitato Etico Fondazione Umberto Veronesi, *Gene-drive e responsabilità ecologica. Parere del Comitato Etico a favore della sperimentazione con popolazioni di zanzare geneticamente modificate, cit.*

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