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Gene drive technologies and global health: a bioethical framework for vector control in contexts of inequality

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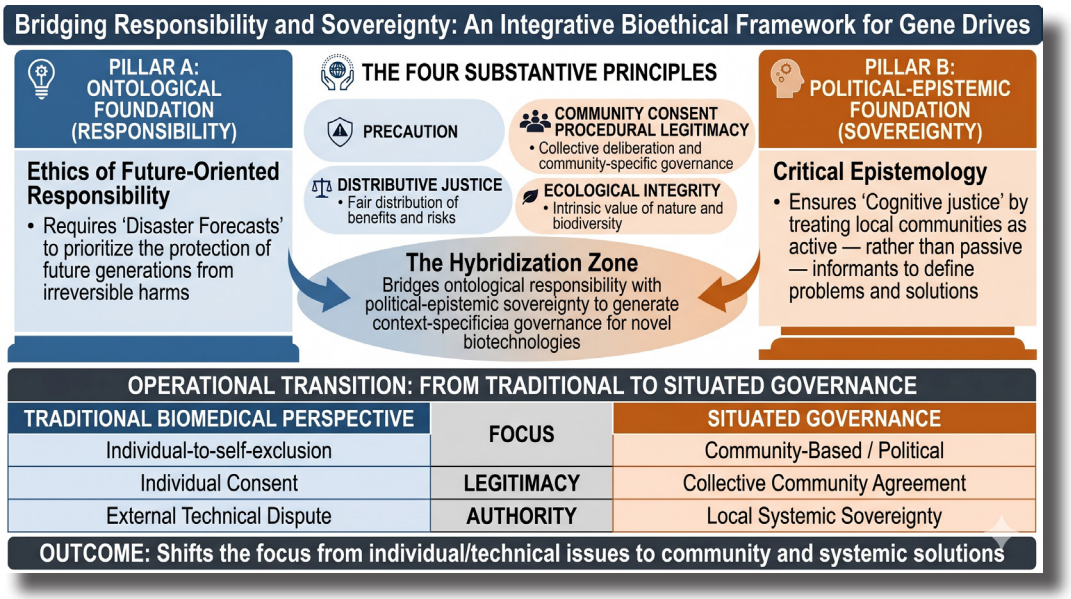
Highlights

- *Gene drive technologies represent an unprecedented form of human intervention in nature, capable of autonomously spreading genetic modifications through wild populations.*
- *The ethical, epistemological, and geopolitical implications of gene drives reveal structural inequalities between the Global North and Global South in knowledge production and risk distribution.*
- *Classical bioethical principles require reinterpretation to address collective, ecological, and intergenerational dimensions of technological responsibility.*
- *The article proposes an integrative bioethical framework grounded in global justice, epistemic sovereignty, precaution, and ecological integrity to ensure the moral legitimacy of biotechnological innovation.*

Graphical Abstract



Abstract

Vector-borne diseases remain a major global health burden, with dengue reaching 14.6 million cases and malaria causing nearly 600,000 deaths in 2024, disproportionately affecting populations in the Global South. Gene drive technologies based on CRISPR-Cas9 have emerged as a disruptive approach to vector control, yet their governance is marked by regulatory and epistemic asymmetries. This study aims to formulate an integrative bioethical framework from which operational criteria can be derived for regulating gene drive technologies in contexts of epidemiological urgency. A theoretical-normative methodology was applied, integrating epidemiological evidence with critical bioethics, decolonial epistemology, and international biosafety law. The analysis develops a framework that combines responsibility ethics with epistemic sovereignty, from which a matrix of distributive justice indicators and community consultation protocols is derived for regulatory application in the Global South. The findings indicate that existing regulatory instruments, particularly the Cartagena Protocol, present limitations in addressing irreversibility, transboundary risks, and liability. The proposed framework provides a structured approach to incorporate precaution, justice, and procedural legitimacy into decision-making processes. These results suggest that effective governance of gene drive technologies requires integrating scientific assessment with socially grounded criteria, contributing to more robust and context-sensitive regulatory practices in global health.

Keywords: Gene drive. Epistemic sovereignty. Vector-borne diseases. Precautionary principle. Distributive justice.

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INTRODUCTION

Vector-borne diseases have reached an epidemiological magnitude in the last decade that exceeds the capacities of conventional health systems, particularly in the tropical and subtropical regions of the Global South[1]. The year 2024 marked a historic milestone with more than 14.6 million cases of dengue reported globally and nearly 600,000 deaths per year attributable to malaria, figures that confirm the structural persistence of a geography of vulnerability that is not exclusively due to biological factors but to deep-rooted social, economic and climatic determinations[2,3,4]. In this context of health crisis, gene drive technologies based on the CRISPR-Cas9 platform have emerged as a disruptive biotechnological promise for vector control, offering the unprecedented ability to propagate genetic modifications through wild populations through biased inheritance mechanisms that far exceed Mendelian rates[5,6]. However, the mere technical power of the tool does not resolve, but rather exacerbates, a web of ethical, epistemological, ecological, and geopolitical tensions that run through global biomedical research[7,8].

The development of these technologies has highlighted limitations in existing ethical and regulatory frameworks. Gene drive technologies are predominantly developed in institutional contexts of the Global North, with their own epistemic rationalities and funding priorities, but are intended to be deployed in ecosystems and communities in the Global South, without any integrative bioethical frameworks or binding governance mechanisms capable of simultaneously ensuring distributive justice, ecological integrity, and epistemic sovereignty of affected populations[9,10]. Such a gap is not a technical anomaly that can be overcome through greater bureaucratic coordination, but rather the contemporary manifestation of historical patterns of coloniality of knowledge and power[11,12].

The general objective of this article is to formulate an integrative bioethical framework from which operational criteria are derived for the regulation of gene drive technologies in the Global South in the face of the epidemiological urgency of vector-borne diseases. To this end, the text is structured in four substantive sections: the first supports the epidemiological urgency and delimits the technical contrast between Mendelian heritage and biased inheritance; the second problematizes governance from the political economy and coloniality of knowledge; the third constitutes the normative architecture of the integrative bioethical framework; and the fourth operationalizes this framework through a matrix of indicators and consultation protocols aimed at regulatory agencies in the Global South.

Epidemiological urgency and technical contrast between Mendelian inheritance and biased inheritance

The global burden of vector-borne diseases has experienced a sustained expansion over the last two decades, configuring an epidemiological scenario that the World Health Organization has classified as a level three health emergency in the specific case of dengue[1]. During 2024, more than 14.6 million cases of dengue were reported in more than one hundred countries, with more than 12,000 associated deaths, figures that double the records of the previous year and confirm the exponential trend observed since 2021[2]. The Region of the Americas accounted for more than 90 percent of global cases, with Brazil alone reporting more than ten million cases and 6,321 deaths, which has led to characterizing this crisis as a "poordemic" or pandemic of the poor[2,3].

In parallel, the World Malaria Report 2024 documented approximately 263 million cases and 597,000 deaths from malaria, with 94 percent of cases and 95 percent of deaths concentrated in the African Region, with children under five years of age contributing nearly three-quarters of mortality[1]. Global bioethics frameworks emphasize that the vulnerability to infectious risks is often exacerbated by profound socio-historical marginalization[13]. This geographical and demographic distribution of the burden confirms that vector-borne diseases fall, in a structurally disproportionate manner, on historically impoverished populations[14]. To this burden must be added the active circulation of chikungunya, Zika, yellow fever and, more recently, Oropouche, together with the sustained deterioration in the effectiveness of conventional interventions due to insecticide resistance, unplanned urbanization and climate change[15].

Factors that explain the current epidemiological expansion include the increasing resistance of vectors to pyrethroid insecticides, the shortening of the viral incubation period induced by global warming, and the re-emergence of viral serotypes against which populations lack prior immunity[2,3]. In the Brazilian case, the re-emergence of the DEN-3 serotype after fifteen years of absence contributed decisively to the 2024 outbreak, while traditional chemical control strategies have shown between 1 and 20 percent effectiveness in eradicating adult mosquitoes[3,16]. Against this backdrop, conventional vector control has demonstrated structural limits to interrupt transmission cycles in contexts of high epidemic load.

Faced with these limitations, biotechnological

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strategies have emerged as complementary tools with varying degrees of technical disruption. A first category corresponds to strategies based on conventional Mendelian inheritance, among which the use of the endosymbiont bacterium *Wolbachia* (wMel strain) introduced into *Aedes aegypti* populations stands out[17]. This intervention operates through two main biological mechanisms: cytoplasmic incompatibility, which favors the spread of infected females, and pathogen inhibition, which reduces the vectorial competence of the mosquito to transmit arboviruses[15]. Maternal transmission close to 100 percent and phenotypic stability documented over a decade in Australian populations underpin the technical feasibility of this strategy under favorable environmental conditions[17].

However, field results in the Global South have shown significant heterogeneity. In Niterói, Brazil, releases of wMel-infected mosquitoes were able to establish a prevalence of more than 95 percent and an 89 percent reduction in dengue incidence after seven years of intervention[18]. In contrast, the Rio de Janeiro program achieved only a 38 percent reduction for dengue and 10 percent for chikungunya, with a suboptimal invasion level of 32 percent[19]. In Medellín, Colombia, post-release studies identified a residual prevalence of between 9.5 and 33.2 percent, well below the 80 percent threshold considered necessary for robust epidemiological protection[20].

Additional studies have documented specific technical limitations of the *Wolbachia* strategy. The viral blockade of the wMel strain is compromised by high circulating viral loads, allowing the infection, dissemination and presence of the dengue virus in the saliva of mosquitoes colonized with the bacterium[21]. Additionally, the biological fitness cost associated with egg resistance under environmental stress, as well as the thermal sensitivity of the bacterium during larval development, can cause introgression collapse when they coincide with aggressive chemical interventions or tropical heat waves[22]. The natural presence of endogenous *Wolbachia* strains in wild populations of *Anopheles* and *Aedes* can also generate unwanted bidirectional cytoplasmic incompatibility phenomena[23].

A second biotechnological category corresponds to biased inheritance systems, specifically gene drives based on the CRISPR-Cas9 platform. Unlike the *Wolbachia* strategy, which operates under the principles of Mendelian inheritance with a maximum transmission of 50 percent per generation, gene drives are designed to achieve inheritance rates close to 100 percent through the molecular conversion mechanism called homing[5]. This mechanism allows a modified genetic element to actively copy the homologous chromosome during gametogenesis, spreading autonomously through a wild population within a few generations[6].

Experimental gene drive systems developed for *Anopheles gambiae* have directed Cas9 nuclease activity towards female fertility genes such as AGAP007280, achieving transmission rates of between 91.4 and 99.6 percent[5]. Bioinformatic analysis of 1,280 mosquito genomes has identified more than 51 million potential Cas9 target sites in the *An. gambiae* genome, with approximately 90 percent of protein-coding genes containing at least one highly conserved site[6]. The technical efficiency of the platform is consequently far superior to that of any previous vector control tool.

However, the most distinctive technical characteristic of gene drives lies not in their efficiency, but in their intentional persistence and their ability to spread autonomously, irreversibly, and across borders[7,8]. Unlike conventional modified organisms designed for confinement, gene drive systems are designed to remain indefinitely in the ecosystem, crossing jurisdictional boundaries without further human intervention[24]. This technical singularity categorically differentiates gene drives from strategies based on Mendelian inheritance and establishes a new threshold of complexity for risk assessment, different from that applicable to any previous biotechnology[25].

The characterization of the epidemiological urgency and the technical contrast between Mendelian inheritance strategies and biased inheritance systems not only show a qualitative leap in the capacity for biotechnological intervention on vector populations, but also reveal a shift of the problem from the strictly biomedical field to the terrain of the structural implications of its deployment. Such a shift requires placing analysis on a different scale, where the conditions of production, control and application of knowledge acquire explanatory centrality. Consequently, the following section introduces an examination of the political economy and coloniality of knowledge that shape the governance of gene drives, in order to understand how global asymmetries condition both the definition of risk and the legitimacy of regulatory decisions.

Political economy and coloniality of knowledge in the governance of genetic drives

The contemporary governance of gene drive technologies cannot be understood as a technically neutral field, but rather as an arena where asymmetric flows of capital, knowledge, patents, and decision-making power intersect[26]. Mapping the actors involved in the development, financing, and evaluation of these technologies reveals a systematic

geographic concentration: research centers, patent platforms, major funders, and dominant regulatory bodies are located in institutions in the Global North, while recipient ecosystems and directly affected communities are located in territories in the Global South[27,28].

Far from being fortuitous, such a spatial distribution of techno-scientific power is not accidental. It constitutes a contemporary manifestation of the modern, Eurocentric global pattern of capitalist power that has organized the global production of knowledge since the historical constitution of America as a colonial periphery[11]. In this pattern, coloniality operates as a structural element that racially classifies the world's population and legitimizes the hegemony of Eurocentric knowledge as the only valid rationality[29]. International capital, according to this analysis, becomes global precisely through the establishment of a division of labor and knowledge that assigns the North the production of innovation and the South the function of receiving laboratory[30].

As an empirical illustration of this structure, the political economy of gene drive technologies clearly illustrates this configuration. Although 49 of the 55 African Union member states have ratified the Cartagena Protocol, only 12 have operational biosafety laws and functional institutional capacities to evaluate emerging technologies[27]. Most African countries currently lack specific regulatory requirements for the deployment of gene drive modified mosquitoes[24]. This regulatory asymmetry does not represent a technical deficit that can be overcome with greater assistance, but rather an unequal distribution of institutional capacities derived from historical processes of structural dependence[31].

Reinforcing this asymmetry, the concentration of biotechnology patents reinforces this asymmetry. CRISPR-Cas9-based gene drive systems are protected by a network of intellectual property rights predominantly controlled by institutions in high-income countries, which constitutes what has been called "resource privilege" in the global economic order: the legal power to transfer biotechnological goods and set the terms of their use regardless of the local contexts of application[31]. This configuration replicates, on a biotechnological scale, the logic of the double institutional standard that assigns different minimum criteria of justice to national and global orders[31].

From a perspective of theoretical deepening, the theory of the coloniality of knowledge allows us to identify an operation deeper than mere economic concentration: the abysmal thinking that characterizes Western modernity draws radical and invisible lines dividing social reality between a metropolitan side and a colonial side[12]. In the field of knowledge, this abysmal thinking consists of granting modern science the monopoly of the universal distinction between the true and the false, relegating popular, peasant or indigenous knowledge to the category of beliefs or "raw materials" for research[12]. Applied to the regulation of genetic impulses, this abyssal line produces the systematic invisibilization of local ecological knowledge about the intervened ecosystems[30].

As an analytical consequence of the above, the marginalization of local knowledge in risk assessment processes can be characterized, in analytical terms, as a form of dual-dimensional epistemic injustice[32]. On the one hand, there is a preventive testimonial injustice when actors from the Global South are summoned as objects of intervention but not as subjects of enunciation with authority to define the terms of the problem, which reduces the affected populations from the category of "informants" to the condition of "sources of information"[32,33]. On the other hand, a structural hermeneutical injustice operates when international regulatory frameworks lack the conceptual resources necessary to articulate the ethical, ecological, and cosmological concerns of host communities on their own terms[32].

Hence, the double epistemic injustice is not peripheral to the regulatory problem, but constitutes its structural core. Recent empirical studies with civil society organizations in Tanzania have documented how local concerns about legal accountability, technical sovereignty, and the risk of technological neocolonialism are inseparable from any properly technical assessment of gene drive[9]. The voices collected in this study clearly express that "Africa is in a subordinate position" and that "if all decisions are made outside Africa", the very legitimacy of the technology is compromised[9].

In close connection with this epistemic dimension, the political economy of risk aggravates this configuration. The geographical distribution of field trials with genetically modified mosquitoes shows a systematic concentration in countries in the Global South, while regulatory frameworks, patent platforms, and decision-making centers remain located in the North[28]. The potential benefits of the technology, expressed in the prospective reduction of the burden of malaria or dengue, would fall on populations in the South, but the risks of irreversible ecological consequences would also be territorially concentrated there[26]. This asymmetry in the distribution of benefits, risks and decision-making power constitutes a distributive injustice of the first order that operates long before any experimental liberation[31].

From the procedural angle, the procedural analysis of risk assessments reinforces this reading. The choice of endpoints of the assessment, the defini-

tion of what counts as acceptable harm, and the selection of analysis methodologies carry a normative weight (ethical, political, socioeconomic, or cultural) that regulatory agencies tend to present under a veil of scientific neutrality[25]. The "procedural validity" of the assessment, understood as the quality of the analysis process in terms of openness, transparency, and inclusiveness, is as important as or more important than the "substantive validity" of technical results, especially under conditions of high uncertainty such as those that characterize genetic drives[25].

In the light of this interpretative framework, in this framework, the regulatory gaps in the Cartagena Protocol acquire a specific structural significance. Although the Protocol is the main binding international instrument on biosecurity, it was designed under paradigms prior to biased inheritance systems[34]. Article 17, on involuntary transboundary movements, does not provide for mechanisms to respond to the systemic irreversibility of gene drives, while Article 27 establishes only a procedural mandate for the future development of liability and redress rules, without establishing a binding regime[7,34]. These gaps are not minor technical defects, but manifestations of the structural asymmetry that characterizes the global biotechnological order[28].

Therefore, the assessment of gene drives cannot be limited to conventional regulatory frameworks or purely technical biosafety criteria. Rather, it is necessary to build a normative framework capable of integrating ethical, political and epistemic considerations in contexts of profound global inequality. This demand leads directly to the formulation of an integrative bioethical framework that articulates intergenerational responsibility and epistemic sovereignty as complementary principles. Therefore, the following section develops the conceptual architecture of this framework, establishing its philosophical foundations and its substantive principles.

Architecture of an Integrative Bioethical Framework: Responsibility and Epistemic Sovereignty

The construction of an integrative bioethical framework for the regulation of genetic impulses requires articulating two philosophical strands that are usually presented as divergent: the ethics of future-oriented responsibility, developed from Western philosophy in the face of technological civilization, and the critical epistemology of the South, which claims the sovereignty of local knowledge as a condition of global cognitive justice[12,35]. Far from being incompatible, these aspects are complementary in the specific case of disruptive biotechnologies whose effects cross territorial and generational boundaries[36].

From this conceptual framework, the first pillar of the proposed framework is based on the principle of responsibility, whose normative core establishes an unprecedented categorical imperative for modern technological action: to act in such a way that the effects of human actions are compatible with the permanence of authentic human life on Earth[35]. This ontological imperative derives from the observation that contemporary technology has generated a scale of impact that renders the traditional ethics of simultaneity obsolete, demanding an ethics of the future based on the heuristic of fear[35]. The perception of potential evil, according to this approach, is epistemologically more direct and politically more pressing than the perception of the promised good, which forces us to consult fears rather than desires in order to discover the values that must be effectively protected[35].

Under this specific application key, applied to gene drives, the principle of responsibility imposes a normative priority of the "disaster forecast" over the "success forecast" when what is at stake is of absolute or irreversible magnitude[35]. Given that the defining technical characteristic of gene drive systems is precisely their capacity for autonomous, irreversible, and transboundary propagation, the uncertainty associated with their systemic ecological effects cannot be treated as an epistemic gap that can be closed by further research, but as a constitutive condition that activates moral obligations of enhanced precaution[7,36].

Delving into the normative implications of this principle, the responsibility that emanates from this principle is, moreover, univocal and not reciprocal. Unlike contractual ethics based on the reciprocity of rights and duties, responsibility towards future generations and ecosystems cannot be based on a bilateral agreement, since the unborn cannot demand rights and ecosystems cannot negotiate compensation[35]. On the contrary, the obligation is based on the causal power of the present agent over the future, taking as an archetype the structural asymmetry of the father-son relationship[35]. This formulation is particularly relevant in the context of the Global South, where biomedical technologies are deployed on populations and generations that have not participated in their design or given substantive consent[37].

However, when considering its critical scope, the principle of responsibility, taken in its original formulation, presents a significant limitation when applied to the context of colonial asymmetries: it does not problematize the question of who defines risks, who decides which futures deserve protection and from what epistemological framework the fears that activate precaution are articulated[33]. This limitation makes it necessary to integrate a second pillar, which corresponds to epistemic sovereignty under-

stood as a constitutive principle of the bioethical framework[12].

In the face of this limitation, epistemic sovereignty is based on the thesis that there is no global social justice without global cognitive justice, and on the correlative requirement to recognize the plurality of knowledge and the dynamic interconnections between them through an ecology of knowledge[12]. This pillar demands that communities in the Global South are not treated as passive "sources of information", but as active "informants" with full epistemic authority to participate in defining problems, assessing risks, and deliberating about desirable futures[32,33].

In its operational translation, epistemic sovereignty is articulated in three interrelated normative dimensions. The first corresponds to sovereignty in the definition of harm: affected communities must have the authority to establish what counts as a relevant risk and which ecological, cultural or spiritual goods deserve priority protection[13]. The second corresponds to sovereignty in the definition of the method: risk assessment methodologies must be situated and culturally sensitive, incorporating local knowledge systems as legitimate sources of evidence[25]. The third corresponds to sovereignty in decision-making: national and community authorities in the Global South must retain the ultimate power to accept, condition, or reject the deployment of emerging technologies, regardless of external technical or political pressure[9].

From the interaction between both pillars, the hybridization between responsibility and epistemic sovereignty generates a normative architecture that transcends the limitations of both pillars taken in isolation. Responsibility provides the ontological foundation that justifies caution in the face of irreversibility, while epistemic sovereignty provides the political-epistemic foundation that prevents such precaution from being defined unilaterally from external power centers[35,38]. From this hybridization, four substantive principles emerge that constitute the core of the proposed integrative bioethical framework.

As a normative deployment of this architecture, the first substantive principle corresponds to the reinforced precaution against irreversibility. This principle establishes that, in the face of technologies whose defining characteristic is autonomous and uncontainable propagation, the burden of proof must fall on the proponents of the intervention, and that the absence of scientific certainty cannot be invoked to authorize progress, but rather activates additional obligations of containment, reversibility and democratic deliberation[7,9]. The legal formulation of this principle is supported by Article 10, paragraph 6, of the Cartagena Protocol, which codifies precaution as a sovereign power of the importing Party[34].

The second substantive principle corresponds to distributive justice in the allocation of benefits and risks. This principle requires that the territorial, demographic, and intergenerational distribution of technological effects be explicitly problematized in the regulatory assessment, and that communities that assume ecological risks receive proportional health benefits and legal guarantees of reparation for possible damages[31,37]. Distributive justice, understood in this way, is not limited to a question of access to therapies, but encompasses the global architecture of incentives, responsibilities, and sovereignties that structures biotechnological development[39].

On the other hand, the third substantive principle corresponds to procedural legitimacy by Community agreement. This principle states that, since genetic drives modify the shared environment, the individual informed consent model is ethically insufficient and must be complemented by collective deliberation and authorization processes adapted to local governance structures[37,40]. Procedural legitimacy, in this framework, focuses on the moral value of the decision-making process itself, regardless of whether the result is acceptance or rejection of the technology[40].

In articulation with the ecological limits of the intervention, the fourth substantive principle corresponds to ecological integrity as a non-substitutable value. This principle recognizes that intervened ecosystems have an intrinsic value that cannot be reduced to their instrumental function for human health, and that risk assessment must include long-term ecological management dimensions beyond immediate biomedical indicators[35,37]. Ecological integrity operates as a normative limit criterion in the face of population suppression strategies that could generate unpredictable ecological cascades[41].

From an internal coherence perspective, the internal coherence of the integrative framework is sustained by the recognition that the four substantive principles do not operate in a hierarchical manner but in a dialogic manner. Precaution cannot be legitimately exercised without epistemic sovereignty, since the definition of what to fear requires situated hermeneutical resources[32,33]. Distributive justice cannot be achieved without procedural legitimacy, since the equitable allocation of benefits and risks requires inclusive deliberative processes[40]. Ecological integrity cannot be protected without intergenerational responsibility, since its preservation requires an ethic of the future that transcends the immediate horizons of political action[35]. These four principles constitute the normative basis from which it is possible to operationalize specific regulatory criteria[10]. This transition from a traditional biomedical perspective to a situated governance is synthesized in the following comparative analysis (Table 1).

Table 1 - Contrast between Classical Bioethics and the proposed Integrative Bioethical Framework for Gene Drive Technologies.

Dimension	Classical Bioethics (Principalism)	Integrative Bioethical Framework (Proposal)
Subject of Interest	Autonomous individual (Patient/Participant).	Affected community and future generations.
Legitimacy Mechanism	Individual informed consent.	Community agreement and collective deliberation.
Uncertainty Management	Technical risk/benefit analysis.	Heuristics of fear and reinforced precaution against irreversibility.
Justice Approach	Equitable access to health benefits.	Distributive justice of risks and local epistemic sovereignty.
Value of Nature	Instrumental (Resource for human health).	Intrinsic (Non-substitutable ecological integrity).
Power Relation	Scientific and regulatory neutrality.	Recognition of colonial asymmetries and cognitive justice.

Based on the need for practical projection of the argument, the formulation of an integrative bioethical framework, although it provides a robust normative foundation, would lack practical effectiveness if it were not translated into operational criteria capable of guiding specific regulatory decisions. The technical complexity and uncertainty inherent in genetic drives make this translation into verifiable instruments and procedures applicable by agencies in the Global South imperative. In this way, the following section introduces the operationalization of the proposed framework through a matrix of indicators and consultation protocols, aimed at incorporating the principles of precaution, justice, legitimacy and ecological integrity in regulatory practice.

Operationalization of the framework: matrix of indicators and consultation protocols

Translating the regulatory framework into operational criteria applicable by regulatory agencies in the Global South requires the construction of an indicator matrix that articulates the four substantive principles with evaluable dimensions, observable variables, and specific verification procedures. This matrix is not intended to replace the technical discretion of national authorities, but rather to provide a methodological framework that allows integrating bioethical considerations to be incorporated into the procedures for prior informed agreement, risk assessment and post-release management provided for by the Cartagena Protocol[13,34].

The first operational dimension corresponds to the indicators of enhanced precaution. This dimension includes verifiable criteria aimed at confirming that the proponent has performed a thorough characterization of the mechanisms of intentional persistence of the gene drive, including the evaluation of reversal and immunization impulses available prior to any primary release[7]. Specific indicators include the existence of molecular multi-containment safeguards, the documentation of lead times between project publication and field test execution, and the presentation of fault tree analyses that estimate probabilities of damage under "worst-case" scenarios[25].

From a complementary methodological perspective, for the operational evaluation of this dimension, regulatory agencies can adopt the PRRAF framework proposed by the specialized literature, which integrates five procedural criteria: humility, reflexivity, inclusion, anticipation, and procedural validity[25]. Each criterion translates into verifiable questions that must be answered by the proposer prior to authorization, such as: has the range of uncertainties associated with the system been explicitly recognized?, have long-term adverse scenarios been considered?, have stakeholders challenging the proposer's dominant position been consulted?[25] Documentary verification of these dimensions is a precondition for the issuance of any binding regulatory decision.

On a clearly differentiated distributive level, distributive justice requires the development of an explicit analysis of the territorial, demographic and intergenerational distribution of projected benefits and risks, accompanied by binding legal commitments to redress for possible damages[9,31]. Specific indicators include the detailed demographic characterization of recipient populations, the identification of vulnerable groups (women, children, indigenous peoples, dispersed rural communities), and the quantification of mechanisms for accessing health benefits generated by technology[13].

Under this same logic of assigning responsibilities, a critical component of this dimension is the establishment of contingency funds and operational liability regimes that cover irreversible ecological damage, given that the Cartagena Protocol lacks a binding liability regime adequate to the systemic nature of gene drives[34]. Regulatory agencies in the Global South may require, as a precondition for authorization, the provision of financial guarantees by the proponent, the contracting of environmental insurance with cross-border coverage, and the contractual definition of lines of responsibility between developers, financiers, and implementers of the deployment[9,31].

The third operational dimension corresponds to the protocols of community consultation and collective agreement. This dimension requires the procedural codification of participation mechanisms that transcend individual consent and recognize the authori-

ty of recipient communities to accept, condition, or reject interventions[40,42]. The operationalization of this dimension builds on previous documented experiences in Burkina Faso, Mali and Uganda, where the Target Malaria project has developed iterative models of co-development based on three pillars: inclusion, transparency and accountability[43].

Based on such empirical background, consultation protocols must contemplate, at least, the following procedural elements: biogeographic definition of the affected community based on the flight distance of the target vector; translation of scientific concepts into local languages and cultural frameworks; establishment of community monitoring committees with effective authority; and recognition of the right of communities to withdraw their consent at any stage of the process[40,43]. The adoption of community consent does not imply the dissolution of individual consent, but rather its complementation through an appropriate collective mechanism for wide-area environmental interventions[37].

In addition, procedural legitimacy requires the explicit inclusion of critical and dissenting voices in the consultation process. Target Malaria's experience in Burkina Faso with the creation of the "Relay Group" for opposition civil society organizations illustrates the operational possibility of transforming dissent into an input of regulatory robustness, provided that agencies ensure that engagement does not become a mere formality for technological acceptance[10,42]. Verifiable indicators for this dimension include the number and diversity of actors consulted, the documentation of concerns expressed and responses offered, and the existence of mechanisms for appealing controversial decisions.

The indicators of ecological integrity and post-release monitoring are articulated around the post-release monitoring route proposed by the specialized literature for the African context, which requires the prior definition of specific protection objectives (human and animal health, biodiversity and water quality) by local experts[13]. Specific indicators include quantifying the prevalence of gene drive in wild populations, early detection of unforeseen adverse effects on non-target species, and documenting changes in vector population structure and disease transmission patterns[13].

From the demand for technical autonomy, the operationalization of post-release monitoring requires the strengthening of national technical capacities independent of developers and financiers. Empirical evidence collected in Tanzania indicates that local experts perceive the existence of autonomous technical supervision as a fundamental condition, free of conflicts of interest derived from financial or training dependence on the proponents of the technology[9]. Regulatory agencies may require, as part of the authorization process, the transfer of technical capacities, the training of national experts and the creation of open data platforms accessible to both authorities and civil society[27].

In relation to surveillance time horizons, the minimum period of post-release monitoring has been suggested by expert consensus at at least five years, with a significant portion recommending permanent monitoring as long as the technology remains active in the ecosystem[13]. This time frame reflects the technical uniqueness of gene drives compared to conventional modified organisms, whose observation cycles can be completed in much shorter periods[34]. Regulatory agencies in the Global South can incorporate this temporary requirement as an explicit condition of authorization, with periodic review mechanisms that allow interventions to be suspended or modified in the event of the detection of significant adverse effects[13].

The four proposed operational dimensions are integrated into a phased evaluation procedure, analogous to the proposed "decision gate" development path for gene drive research in sub-Saharan Africa[44]. Each phase of the procedure (laboratory, physical containment, limited release, extended release) must validate specific criteria corresponding to each of the four dimensions before allowing progress to the next stage. This staggered structure allows for the incorporation of iterative learning, continuous community review, and the ability to suspend the process at any sign of unmitigated risk[43,44].

In terms of its institutional projection, the concrete applicability of the proposed framework to specific regulatory contexts in the Global South, such as the Agência Nacional de Vigilância Sanitária in Brazil or the National Institute of Health in Peru, depends on the political will of States to incorporate operational criteria into their national regulations through complementary instruments to the Cartagena Protocol[27,28]. Regional harmonization, through blocs such as the African Union, the Andean Community or MERCOSUR, would make it possible to overcome the limitations of strictly national actions in the face of the inherently transboundary nature of gene drives[28].

The operationalization of the integrative bioethical framework through a matrix of indicators transcends the mere normative translation and directly redefines the decision-making criteria in contexts of uncertainty and global inequality. By articulating enhanced precaution, distributive justice, procedural legitimacy, and ecological integrity, the approach shifts assessment from a technical risk analysis to a more rigorous and situated governance. Consequently, the matrix not only strengthens the regulatory capacity of the Global South, but sets a demanding standard according to which every decision must be technically sound, ethically grounded, and politically legitimate.

CONCLUSIONS

The emergence of biased inheritance systems, such as gene drives, suggests a turning point where conventional regulatory tools are insufficient in the face of the urgency of vector-borne diseases. Because of the ability of these technologies to spread autonomously and irreversibly, risk assessment transcends traditional technical biosafety and takes on inescapable political and philosophical dimensions. It is essential to formulate an integrative bioethical framework that responds to the structural asymmetries between those who develop innovation and those who inhabit the recipient ecosystems. The proposal articulates the forward-looking principle of responsibility with the requirement of epistemic sovereignty, so that precaution in the face of ecological uncertainty is complemented by the need for local communities to have the legitimate authority to define risks and assess the relevance of biotechnological interventions in their own territories.

In the field of global health, this regulatory reconfiguration has profound implications for international health governance. Biotechnological interventions tend to reproduce logics of coloniality of knowledge when they are designed from external centers of power that ignore local sociocultural realities. Therefore, the legitimacy of any technological deployment seems to depend on a transition to models based on distributive and procedural justice. The aforementioned requires abandoning the logic of vertical imposition and moving towards a co-development where the acceptance of technology transcends the individual scale to be consolidated through a broad community agreement. From this perspective, global health is conceived not only as the mere reduction of morbidity indicators, but as a space for symmetrical intercultural dialogue that simultaneously protects social equity and ecological integrity.

The development of this ethical paradigm outlines a future research agenda aimed at consolidating truly adaptive governance. It is a priority to research and improve robust mechanisms for social participation, ensuring that community engagement is structured from the early stages of design and is not reduced to an administrative procedure to facilitate the acceptance of technology. Likewise, the development of long-term ecological monitoring protocols that are managed by local experts and kept free of conflicts of interest is required. The exploration of strategies for regional regulatory harmonization represents another crucial vector of study, given that the intervened ecosystems do not recognize political jurisdictions and the effectiveness of any precautionary measures will depend on coordinated responses and strengthened institutions in the Global South.

CRediT author statement

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Declaration of competing interest

The author declares that he or she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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