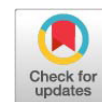


Research Article



The Future of *Macaca* Primate Supply Chain: Integrating Conservation and Research Demands in Indonesia

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Abstract | Indonesia represents a key geographic node in the global biomedical supply chain, supported by a long-standing history of non-human primate (NHP) exports since the 1970s and established closed-colony breeding infrastructure. This comprehensive review evaluates the operational future of this supply chain by systematically integrating wild population conservation mandates with the rigorous requirements of international translational and preclinical research. Recent ecological shifts, followed by the IUCN's 2022 reclassification of *Macaca fascicularis* as Endangered and the subsequent implementation of data-driven Non-Detrimental Findings (NDF) under CITES guidelines, underscore the urgent need for sophisticated population management. The global biomedical community faces a severe shortage of non-human primates (NHPs), highlighting the need to transition from wild-caught harvesting to highly controlled, closed-colony captive breeding systems. While in-situ habitat protection and conflict mitigation are foundational for wild populations, transitioning the biomedical procurement pathway from wild-caught harvesting to closed-colony captive breeding serves as a mandatory ex-situ strategy to eliminate wild extraction pressures on this newly endangered species. Facilities capable of generating certified Specific Pathogen-Free (SPF) colonies eliminate latent viral variables (e.g., simian retrovirus), thereby reducing baseline immunological variance, minimizing statistical noise, and significantly enhancing the reproducibility and power of preclinical trials. Furthermore, Indonesia's dual-layered regulatory framework—which integrates strict domestic veterinary welfare legislation with international CITES scientific quotas (Non-Detrimental Findings)—ensures compliance with the 3Rs principles (Replacement, Reduction, and Refinement). Operationalizing this national transition, we recommend establishing national fiscal incentives for high-barrier SPF breeding infrastructure and standardizing Institutional Animal Care and Use Committee (IACUC) audits across domestic facilities.

Keywords | Animals, Extinct species, Genetic resources, Global supply chain, Preclinical reproducibility, Specific. Pathogen-Free

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INTRODUCTION

The Republic of Indonesia stands as a prominent global megadiverse epicenter, harboring an exceptionally rich national primate heritage that encompasses approximately 70 distinct species across the archipelago (BRIN and KLHK, 2023). Characterized by complex biogeographical divisions such as Sundaland and the Wallacea transition zone, the Indonesian archipelago has fostered unique evolutionary lineages, among which the genus *Macaca* represents one of the most widely distributed and ecologically adaptive mammalian taxa (Putri *et al.*, 2024). Long-tailed macaques (*Macaca fascicularis*) and pig-tailed macaques (*Macaca nemestrina*) exhibit intricate social dynamics, high behavioral flexibility, and robust survival mechanisms across diverse forest canopies and anthropogenic fringes (Sohara *et al.*, 2023). Historically, these species were perceived as ubiquitously abundant due to their high visibility in human-modified landscapes; however, recent demographic data reveal a genuine population decline exceeding 30% over the last three decades, driven by accelerated habitat loss and unsustainable historical extraction (Sohara *et al.*, 2023).

Over the past several decades, the physiological, anatomical, and immunological proximity of non-human primates (NHPs) to humans has rendered them indispensable within translational medicine and advanced preclinical trials (BRIN and KLHK, 2023; Sohara *et al.*, 2023). Genus *Macaca*, in particular, serves as the critical baseline for assessing vaccine efficacy, neurodegenerative disease progression, and complex pharmacokinetic profiling before human clinical deployment. The global primate supply chain experienced a pivotal structural shock in January 2020 when China—historically supplying over 60% of international research primates—enacted a complete ban on wildlife exports. The structural vulnerability of global healthcare infrastructure became acutely apparent during the COVID-19 pandemic, driven by a dual crisis: an unprecedented surge in demand for accelerated vaccine validation and a severe global supply deficit triggered by China's 2020 primate export ban alongside international shipping restrictions (Sohara

et al., 2023; Cyranoski, 2016). This global operational shift away from wild-caught harvesting toward purpose-bred closed colonies is fundamentally accelerated by stringent international regulatory mandates. Specifically, European Union Directive 2010/63/EU (under Article 10) enforced a mandatory transition requiring all laboratory primates to be second-generation or higher (F2+) captive-bred by November 2022, while the United States National Institutes of Health (NIH) policy directives restricted federal research funding strictly to purpose-bred subjects (EU, 2010; NIH, 2018). These specific international legal requirements define the absolute market standards that Indonesia's export strategy must satisfy.

However, the intersection of expanding international research demands and local anthropogenic pressures has driven wild macaque populations into a critical conservation crisis. The dramatic reclassification of *M. fascicularis* to "Endangered" status by the International Union for Conservation of Nature (IUCN) in 2022 marked a profound shift in primate management and global acquisition strategies (Utami *et al.*, 2025). Wild stocks are increasingly threatened by widespread anthropogenic habitat fragmentation, agricultural monoculture expansion and severe human-wildlife conflicts that alter natural demographics and heighten bidirectional pathogen transmission risks (Sohara *et al.*, 2023; Utami *et al.*, 2025). Consequently, relying on wild-caught harvesting is no longer scientifically, legally, or ethically sustainable, as it severely compromises animal welfare, violates international publishing guidelines, and threatens the long-term ecological balance of native ecosystems (BRIN and KLHK, 2023). Empirical models from major exporting nations like Mauritius demonstrate that scaling up closed-colony infrastructure directly facilitates the reduction of wild harvesting by satisfying international buyers who are legally restricted from purchasing wild-caught stocks (Kubersky and Hernandez-Alonzo, 2025).

Operating under CITES Appendix II, Indonesia's Non-Detrimental Findings (NDF) framework functions via a strict dual-authority mechanism, where the scientific

authority (BRIN) establishes localized capture limits based on dynamic population models, differing from other states by legally mandating a 15% spatial exclusion zone across natural habitats to halt over-exploitation (BRIN and KLHK, 2023). This administrative evolution serves as a vital tool to balance the socio-economic value of scientific exports with international conservation pledges (BRIN and KLHK, 2023; Setiawan *et al.*, 2023). Despite individual studies addressing wild ecology or laboratory protocols in isolation, a significant knowledge gap remains regarding how a megadiverse nation can operationally harmonize ex-situ Specific Pathogen-Free (SPF) captive-breeding supply chains with newly elevated Endangered conservation mandates under dynamic CITES NDF frameworks. Therefore, this review aims to provide a comprehensive analysis of the future of the *Macaca* supply chain in Indonesia, exploring how the strategic integration of strict ecological policies, advanced closed-colony captive breeding systems, and unyielding animal welfare standards can successfully sustain global translational research while safeguarding national scientific sovereignty.

DISTRIBUTION AND POPULATION STATUS OF MACACA IN INDONESIA

The geographical distribution of the *Macaca* population across the Indonesian archipelago demonstrates remarkable biogeographical diversity, influenced by Sundaland ecology and Wallacean evolutionary isolation. The island of Sumatra serves as the largest natural reservoir for both *Macaca fascicularis* and *Macaca nemestrina*. Detailed demographic profiles, population estimates, and regional densities across the major islands are meticulously organized in Table 1. It must be critically noted that a direct quantitative cross-comparison of these regional datasets is constrained by historical heterogeneities in field methodologies. Specifically, traditional distance-sampling line transects calculate direct encounter rates along linear pathways, whereas modern Spatially Explicit Capture-Recapture (SECR) and Minimum Convex Polygon (MCP) models apply spatial probability density functions across spatial grids (Buckland *et al.*, 2010). Merging these distinct analytical frameworks without statistical calibration introduces potential spatial bias representing a systemic limitation in national primate monitoring that this review addresses by explicitly mapping the underlying data collection methods (Miller *et al.*, 2013).

Analysis of the lowlands of South Sumatra reveals a massive demographic reservoir, with macro-scale landscape extrapolation estimates approaching 300,000 individuals (estimated 95% confidence interval: 220,000–380,000), underscoring the region's profound capacity to sustain long-term genetic viability (Setiawan *et al.*, 2024). Riparian ecosystems within this territory, such as

the Calik River basin, exhibit dense riverbank clustering with over a thousand recorded individuals, demonstrating that continuous gallery forests serve as vital ecological lifelines for seasonal foraging and predator avoidance (Setiawan *et al.*, 2023). However, readers must account for edge-effect sampling bias, as boat-based riparian surveys tend to overestimate broader landscape-level densities due to diurnal primate clustering along riverine foraging corridors. In West Sumatra and Jambi, both *M. fascicularis* and *M. nemestrina* are experiencing rapid habitat shifts. Their high cognitive plasticity allows them to exploit urban fringes and agricultural monocultures; while this confirms an impressive evolutionary tolerance to human disturbance, it drastically escalates the frequency of human-primate interfaces, resulting in crop raiding, economic loss, and an increased risk of bidirectional pathogen transmission (Sohara *et al.*, 2023; Utami *et al.*, 2025).

Furthermore, the data compiled spans a broad temporal range (2009–2025). While older baselines remain essential due to the lack of recent systematic censuses in deep-forest interiors, readers must interpret these figures with caution as significant land-use changes may have induced unrecorded demographic shifts prior to the 2022 IUCN reclassification (Buckland *et al.*, 2010). Metapopulation trajectories across Indonesia exhibit a clear long-term downward trend, characterized by a macro-level decline exceeding 30% over the last three generations (approximately 36 years), which directly aligns with Criterion A2ab of the IUCN 2022 Endangered reclassification metrics (Hansen *et al.*, 2022). While populations within fenced sanctuaries may appear locally stable, unprotected populations face severe, ongoing contractions driven by active habitat conversion (Curtis *et al.*, 2018).

COMPARATIVE CONSERVATION AND BIOMEDICAL DISTINCTIONS BETWEEN *M. FASCICULARIS* AND *M. NEMESTRINA*

Macaca fascicularis (Endangered) and *Macaca nemestrina* (Vulnerable) must be clearly decoupled regarding both supply chain management and laboratory application. Structurally, *M. nemestrina* prefers interior primary forest matrices and exhibits lower reproductive outputs, rendering its wild populations highly sensitive to logging (Yanuar *et al.*, 2009). Therapeutically, while *M. fascicularis* remains the primary global model for vaccine toxicology, *M. nemestrina* serves as an irreplaceable model for specialized neurobehavioral paradigms and cognitive retroviral pathobiology due to its distinct neurological structures and high susceptibility to simian immunodeficiency viruses (Agy *et al.*, 1992).

Conversely, the island of Java presents a contrasting demographic landscape defined by severe habitat

Table 1: Comprehensive population estimates and densities of the genus macaca across indonesia.

Island/Region	Species	Specific Location	Estimated Population / Density Parameters	Methodology Used	References
Sumatra	Macaca fascicularis	Lowlands of South Sumatra	4,316 recorded; Estimated total of 300,000 individuals (95% CI: 220,000 – 380,000)	Line-transect sampling and Extrapolation	(Setiawan <i>et al.</i> , 2024)
		Calik River, South Sumatra	1,194 individuals (along 115 km of riverbanks)	Riparian boat survey	(Setiawan <i>et al.</i> , 2023)
		Kerinci-Seblat National Park	Density of 4–5 individuals/km ²	Line-transect distance sampling	(Yanuar <i>et al.</i> , 2009)
		Padang City, West Sumatra	32 group encounter points; Wide urban-fringe distribution	Direct encounter mapping	(Utami <i>et al.</i> , 2025)
		Jambi Province	High occupancy in Mangroves, Palm Oil Plantations, and Secondary Forests	Point count surveys	(Putri <i>et al.</i> , 2024)
Sumatra	Macaca fascicularis	Tabuan Island, Lampung, Southern Sumatra	6,523 individuals (high density isolated insular colony)	Concentration count and Sweep sampling	(Hasibuan <i>et al.</i> , 2025)
		Legundi Island, Lampung, Southern Sumatra	3,415 individuals (monitored insular ecosystem)	Concentration count and Sweep sampling	(Hasibuan <i>et al.</i> , 2025)
		Punti Kayu Nature Tourism Park, Palembang, South Sumatra	247 individuals (urban fragment population)	Total group headcount	(BRIN and KLHK, 2023)
	Macaca nemestrina	Kerinci-Seblat National Park	Density of 13–14 individuals/km ² (pristine forest interior)	Line-transect distance sampling	(Yanuar <i>et al.</i> , 2009)
		Sitinjau Lauik, Padang, West Sumatra	Average of 18 individuals/group (anthropogenic interface)	Direct group monitoring	(Sohara <i>et al.</i> , 2023)
Java	Macaca fascicularis	Baluran National Park, East Java	10,350 individuals (High Density: 41,4 individuals/km ²)	SECR Modeling over 100% MCP	(Hansen <i>et al.</i> , 2019)
		Deli Island, Pandeglang, Banten	4,860 individuals (established semi-captive introduced colony)	Total population census	(Rifqi <i>et al.</i> , 2023)
		Gunung Ciremai National Park, West Java	197 individuals; Hyper-concentrated micro-density of 18.9 individuals/ha (1,890/km ² at hotspots)	Line-transect distance sampling	(Fajrin <i>et al.</i> , 2022)
		Central Java (15 Regencies)	Aggregated into thousands of individuals (severe conflict zones)	Questionnaire and Conflict point mapping	(Fitria <i>et al.</i> , 2020)
		Grojogan Sewu, Karanganyar, Central Java	"Patapan" group consisting of 79 highly habituated individuals	Direct focus group tracking	(Syah, 2020)
Java	Macaca fascicularis	Tinjil Island, Pandeglang, Banten	642 – 661 individuals (historical natural breeding reserve)	Capture-recapture and Mark-resight	(BRIN and KLHK, 2023)
		Gunung Kapur, Bogor, West Java	245 individuals (karst ecosystem fragment)	Line-transect sampling	(BRIN and KLHK, 2023)
Kalimantan	Macaca fascicularis	Tanjung Puting National Park, Central Kalimantan	13,321 – 23,100 individuals (highly dependent on riverine systems)	Riparian boat transects	(Gumert <i>et al.</i> , 2012)
Sulawesi	Macaca nigra	Tangkoko Conservation Area, North Sulawesi	Density: 68.7 individuals/km ²	Line-transect distance sampling	(BRIN and KLHK, 2023)
	Macaca tonkeana	Central Sulawesi	Density of 3–5 individuals/km ²	Line-transect sampling	(BRIN and KLHK, 2023)
	Macaca maura	Karaenta Karst Forest, South Sulawesi	Average of 92 individuals/km ²	Point-quadrat and Group monitoring	(BRIN and KLHK, 2023)
Sulawesi	Macaca ochreata	Southeast Sulawesi	Group density ranging between 0.97 – 2.0 per km ²	Line-transect sampling	(BRIN and KLHK, 2023)
Nusa Tenggara	Macaca fascicularis	Lemor Botanical Garden, Lombok, NTB	82 individuals partitioned into 4 distinct groups	Direct group count	(Sopana <i>et al.</i> , 2018)
		Kelimutu National Park, Flores, NTT	Average encounter index of 5 individuals/linear km	Encounter rate survey	(Fauzi <i>et al.</i> , 2020)

fragmentation and island biogeography pressures. The exceptionally high population estimate recorded in Baluran National Park hosts a high modeled population estimate exceeding 10,000 individuals, generated via Spatially Explicit Capture-Recapture (SECR) modeling layered over Minimum Convex Polygon boundaries constraints and artificial food subsidies from tourism (Efford, 2004; Hansen *et al.*, 2019). While SECR modeling provides robust density surfaces, its estimates remain sensitive to spatial trap-boundary assumptions and localized animal clustering.

In smaller, isolated forest matrices like Gunung Ciremai National Park, spatial entrapment has elevated localized micro-densities to a critical threshold of 18.9 individuals per hectare (equivalent to a hyper-concentrated micro-density of 1,890 individuals/km² at provisioning hotspots), testing the carrying capacity of the ecosystem and altering natural social dynamics (Fajrin *et al.*, 2022). This localized hyper-densification represents a profound ecological paradox; it is not an indicator of metapopulation expansion, but rather a direct consequence of the ‘compression effect’ (crowding effect). Forced out of surrounding deforested landscapes, macaques are artificially compressed into remaining protected isolates, which accelerates localized resource depletion, elevates pathogen transmission, and directly validates their global ‘Endangered’ status (Estrada *et al.*, 2017; Nunn and Altizer, 2006). To contextualize this scale, baseline primatological models suggest that natural, unassisted carrying capacities for *M. fascicularis* peak at 10–15 individuals/km² in undisturbed ecosystems; macro-landscape densities exceeding the 40 individuals/km² are heavily subsidized by surrounding agricultural crops, whereas extreme micro-densities reaching 1,890 individuals/km² reflect severe spatial entrapment subsidized by human food source (Sha and Hanya, 2013).

To counter these pressures, Indonesia’s strategic deployment of offshore islands—such as Tinjil Island and Deli Island—as natural, semi-captive propagation centers has proven internationally exemplary. These isolated sanctuaries yield thousands of high-health individuals completely insulated from mainland agricultural contaminants and human conflicts (Sohara *et al.*, 2023; Rifqi *et al.*, 2023). Yet, across 15 mainland regencies in Central Java, uncontrolled agricultural expansion continues to spark intense friction, demanding aggressive, data-driven demographic management interventions to mitigate socio-ecological crises (Fitria *et al.*, 2020; Syah and Moh, 2020).

In the vast terrains of Kalimantan and the scattered ecosystems of Nusa Tenggara, population dynamics are highly localized. The long-tailed macaques of Tanjung Puting National Park exhibit strict riverine dependency,

utilizing riparian gallery forests as mandatory nesting platforms and primary foraging highways (Gumert *et al.*, 2012). In stark contrast, the populations throughout Lombok and Flores are structurally isolated, confined to shrinking forest patches and protected botanical enclaves (Fauzi *et al.*, 2020; Sopana *et al.*, 2018). Although these eastern peripheral populations do not match the vast numerical scale observed in Sumatra, they possess immense scientific value. They preserve rare allelic frequencies and morphological variations unique to the Wallacea transition zone, making them indispensable for global mapping of primate evolutionary genetics.

The island of Sulawesi introduces an entirely unique, highly critical dimension to Indonesia’s global primate significance through its extraordinary degree of endemism. Geographically isolated from Sundaland, Sulawesi is the exclusive habitat for distinct species such as the critically vulnerable *Macaca nigra*, *Macaca maura*, and *Macaca tonkeana* (BRIN and KLHK, 2023). Monitored conservation strongholds, such as the Tangkoko Nature Reserve and the Karaenta Karst Forest, are vital to safeguarding these vulnerable populations from extinction caused by illegal hunting and habitat conversion (BRIN and KLHK, 2023). It is important to note that, because of their high conservation value and strict legal protection, Sulawesi endemic macaques (e.g., *Macaca nigra*, *M. maura*, and *M. tonkeana*) are not recognized as standard non-human primate models in commercial biomedical research or vaccine-testing pipelines (Riley, 2010; National Research Council, 2011). Instead, their scientific importance lies primarily in studies of evolutionary biology, comparative genomics, conservation genetics, and disease ecology, where they provide unique insights into primate diversification, host evolution, and emerging infectious diseases (Evans *et al.*, 2003; Riley, 2010; Yan *et al.*, 2025).

While mainland Indonesian long-tailed macaques serve the global market for preclinical toxicology and drug screening, Sulawesi’s endemic macaques act as an irreplaceable living library for advanced comparative genomics, evolutionary biology, and specialized immunology research, solidifying the nation’s diverse scientific sovereignty (Setiawan *et al.*, 2024).

CAPTIVE BREEDING AND WILD POPULATION PARADIGMS

In modern biomedical research, transitioning away from wild-caught primates toward certified, multi-generation purpose-bred animals is no longer optional; it is an essential scientific requirement. Primates born and reared within accredited, closed-colony facilities offer experimental variable control that wild-caught animals simply cannot provide (Bliss-Moreau *et al.*, 2021). The defining benchmark of a sophisticated captive breeding program is its ability

to engineer and sustain certified Specific Pathogen-Free (SPF) cohorts. A standard biomedical SPF designation mandates the absolute exclusion of major latent pathogens, specifically simian type D retrovirus (SRV), simian immunodeficiency virus (SIV), simian T-cell lymphotropic virus (STLV), and Cercopithecine herpesvirus 1 (CHV-1 / Herpes B virus) (Morton *et al.*, 2008). In premier Indonesian facilities, accredited veterinary protocols expand this core panel to include mandatory bi-annual screening for *Mycobacterium tuberculosis* (TB) and Measles virus (*Morbillivirus*), ensuring handler safety and complete colony biosecurity (Sajuthi *et al.*, 2016).

The presence of these latent viruses within wild populations introduces massive scientific risk. Subclinical infections such as Simian Retrovirus (SRV-1 and SRV-2) alter baseline immune status by shifting CD4⁺ and CD8⁺ lymphocyte subpopulation ratios and modulating pro-inflammatory cytokine responses, including IL-2 and IFN- γ (Montiel, 2010; Lerche *et al.*, 2010). Although these infections remain clinically inapparent in wild cohorts, they introduce severe biological variability. This variability skews baseline immunological measurements, generates statistical noise, reduces inter-laboratory reproducibility, and forces investigators to increase sample sizes to achieve statistical significance in preclinical trials (Yee *et al.*, 2022). Consequently, rigorous health screening and the deployment of certified SPF colonies are fundamental for minimizing experimental variability in non-human primate research.

Beyond pathogen control, Indonesia's closed-colony infrastructure preserves an exceptionally valuable genetic asset. Comparative genomic profiling has confirmed that *Macaca fascicularis* populations of Indonesian origin, particularly Sumatran lineages, exhibit significantly higher allelic polymorphism and nucleotide diversity than highly inbred global stocks, such as founder-effect Mauritian cohorts (Kanthaswamy *et al.*, 2013). This genetic richness presents a clear methodological trade-off: while highly homologous, inbred cohorts (such as Mauritian stocks) minimize experimental variance and maximize statistical power during initial target validation, they fail to replicate the broad immunogenetic spectrum of human populations (Bliss-Moreau *et al.*, 2021). Through pioneer institutions like the Primate Research Center (PSSP-IPB), Indonesia has successfully capitalized on this natural biodiversity, establishing closed-colony breeding matrices that deliver standardized, SPF-certified subjects recognized by international regulatory bodies (Sajuthi *et al.*, 2016).

From an economic perspective, establishing and operating a certified SPF closed-colony requires a 3- to 4-fold increase in operational expenditure compared to wild-caught

harvesting. This expenditure premium stems directly from four major operational cost centers:

DIAGNOSTIC TESTING

Bi-annual ELISA and real-time PCR diagnostic panels ranging from USD \$150 to \$300 per animal per screening cycle.

BARRIER FACILITIES

High-efficiency particulate air (HEPA) filtration systems, automated environmental controls, and positive-pressure barrier enclosures.

NUTRITIONAL QUALITY CONTROL

Specialized, irradiated, commercial NHP diets fortified with stabilized vitamin C.

VETERINARY OVERHEAD

Dedicated 24/7 veterinary oversight, full-time animal care technicians, and routine health auditing.

Nonetheless, international biopharmaceutical buyers consistently demonstrate a strong willingness to pay this premium (often exceeding \$10,000–\$15,000 USD per animal), as the catastrophic financial cost of using non-SPF animals that fail mid-trial due to latent viral reactivation far outweighs the initial acquisition premium (Sajuthi *et al.*, 2016; Yee *et al.*, 2022).

Crucially, these captive breeding paradigms must be adjusted when applied to *M. nemestrina*. Reared at a significantly smaller industrial scale due to their larger physical size, slower reproductive index, and distinct socialization requirements, *M. nemestrina* closed-colonies are heavily prioritized for highly specialized neurobehavioral pipelines and cognitive retroviral pathobiology rather than mass toxicology screening. This prioritization relies on their unique central nervous system receptor expression and high susceptibility to simian immunodeficiency viruses (Agy *et al.*, 1992; Morton *et al.*, 2008). This necessitates unique housing densities, distinct isolation boundaries, and unique environmental enrichment programs compared to *M. fascicularis*.

Currently, Indonesia's certified facilities yield a combined output of approximately 2,000 purpose-bred individuals annually. This current output reflects a deliberate structural transition when compared to historical wild-caught harvest quotas, which routinely exceeded 5,000 to 10,000 individuals annually during the 1980s and 1990s (BRIN and KLHK, 2023). While this 2,000-animal capacity cannot single-handedly resolve the global deficit—which currently exceeds 30,000 primates annually following international export halts and shipping disruptions

(Gettayacamin *et al.*, 2018; Estrada and Garber, 2022)—Indonesia's strategic target is clear: establish the nation as a premium supplier of genetically diverse SPF cohorts rather than a low-cost, mass-volume exporter.

Furthermore, closed-colony propagation offers superior biological and operational efficiency. Eradicating endemic pathogens within SPF colonies correlates directly with a dramatic drop in infant mortality rates below 8-10%, compared to wild infant mortality rates exceeding 20-25% (Tanaka *et al.*, 2013). The stability gives international research sponsors a predictable supply chain for long-term clinical development program. Operationally, closed-colony frameworks permit the lifelong tracking of individual animal histories. Facility managers utilize specialized studbook software – such as the Single Population Analysis and Record Keeping System and PedProwl – to monitor kinship coefficients, prevent inbreeding depression and maintain precise pedigree records. The detailed nutritional, genetic, and health logs remain completely absent in wild-caught cohorts (Yasutomi, 2010).

Pivotaly , this shift aligns with the international ethical mandate of the 3Rs (Refinement, Reduction, and Replacement). By eliminating the severe physiological stress, dehydration, and immune shock associated with wild capture and long-distance transport, captive breeding optimizes animal welfare, reducing statistical noise, allowing researchers to achieve statistical significance with fewer animals (Prescott, 2010; Schroeder *et al.*, 2018). A granular comparative assessment of these operational dynamics is detailed in Table 2.

ETHICAL AND REGULATORY LANDSCAPE

The implementation of ethical oversight and regulatory compliance governing the utilization of non-human primates (NHPs) in Indonesia represents a mature integration of national environmental legislation and global animal welfare frameworks (Sajuthi *et al.*, 2016; Gettayacamin *et al.*, 2018). Given the close genetic, physiological, and behavioral alignment of *Macaca fascicularis* with humans, their involvement in translational protocols requires exhaustive, multi-layered ethical screening. Every experimental design must align with the definitive standards set forth in the *Guide for the Care and Use of Laboratory Animals* (NRC, 2011). In Indonesia, this compliance is anchored by the prestigious international accreditation of premier institutions, such as the Primate Research Center (PSSP) LPPM-IPB, by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International (Sajuthi *et al.*, 2016). Maintaining AAALAC certification demands scheduled triennial AAALAC International site re-evaluations coupled with internal unannounced quality assurance audits by a functional Institutional Animal Care and

Use Committee (IACUC), ensuring that the principles of Replacement, Reduction, and Refinement are active operational mandates rather than passive concepts (Burm, 2014; Tardif *et al.*, 2013).

Adherence to the 3Rs (Replacement, Reduction, and Refinement) is an essential operational prerequisite for Indonesian primatology facilities. Research protocols are strictly screened by the IACUC, which mandates a formal “3Rs Justification” for every project; failure to demonstrate that non-animal alternatives or statistical reduction strategies have been considered leads to automatic protocol rejection. This institutional screening ensures that researchers provide documented evidence of active enrichment and pain-minimizing protocols prior to primate use approval (Tardif *et al.*, 2013).

On the domestic front, the legal framework protecting laboratory animal welfare is firmly established under Law of the Republic of Indonesia No. 41/2014 (amending Law No. 18/2009) concerning Livestock and Animal Health (Government of Indonesia, 2014). While Law No. 41/2014 sets general animal health mandates, its application to laboratory research primates is specifically operationalized through Government Regulation (PP) No. 95/2012 concerning Veterinary Public Health and Animal Welfare (PPRI No. 95, 2012). Regarding legal enforcement, a clear distinction exists between domestic animal welfare infractions and criminal wildlife trafficking:

ANIMAL WELFARE VIOLATIONS

Article 91B of Law No. 41/2014 targets domestic animal abuse or institutional negligence resulting in injury, applying administrative sanctions (written warnings, activity suspensions, permit revocations) or minor penal sanctions including imprisonment up to six months and monetary fines (Government of Indonesia, 2014).

WILDLIFE TRAFFICKING AND ILLEGAL CAPTURE

Conversely, unauthorized wild capture, illegal transport, or commercial trafficking of wild primates fall under Law No. 5/1990 on the Conservation of Living Natural Resources and Their Ecosystems (Government of Indonesia, 1990). Violations under this statute represent major criminal offenses subject to severe penalties, including up to five years of imprisonment and statutory criminal fines up to IDR 100 million.

Under these national mandates, facilities must guarantee that laboratory primatology protocols actively protect subjects from pain, fear, distress, and chronic discomfort. This is achieved via the enforcement of standardized veterinary medical care, specialized primate nutrition, and complex, dynamic environmental enrichment regimes— such as puzzle feeders and structural climbing

Table 2: Quantitative comparative analysis of captive breeding vs. wild populations in translational science and preclinical trials.

Operational Parameter	Captive Breeding (AAALAC-Accredited Facilities)	Wild Population (Mainland Wild-Caught)	Methodological Impact on Preclinical Trials
Pathogen Profile	Certified Specific Pathogen-Free (SPF); 0% baseline prevalence for SRV, SIV, STLV, Herpes B, Tuberculosis, and Measles	Uncontrolled exposure 60-80% endemic seroprevalence of latent retroviruses, and zoonoses.	Eliminates subclinical immune activation; reduces unconfounded virology assay failures by >80%
Experimental Rigor	Optimized; variance in baseline immunological values reduced by up to 65% (CV < 15%).	Uncontrolled; baseline Coefficient of Variation (CV) exceeds 45% due to unknown histories.	Minimizes baseline outliers; allows achieving statistical significance with up to 40% smaller sample size
Genetic Integrity	Documented pedigree tracking managed via specialized software; active management of heterozygosity	Completely anonymous; high risk of cryptic population structure and uncontrolled inbreeding.	Permits precise cohort stratification; reduce genetic-driven treatment variance by >50%
Ethical Compliance	Strict adherence to the 3Rs; proactive environmental enrichment and minimized stress.	Severe physical and psychological stress due to capture, confinement, and relocation.	Fulfills stringent global journal mandates and international regulatory approval requirements.
Supply Stability	High predictability; infant mortality strictly stabilized below 8%–10%.	High volatility; natural infant mortality exceeds 20%–25% due to disease and predators.	Guarantees >95% timeline adherence for long-term pharmaceutical testing timelines.
Reproductive Rates & Infant Mortality	Controlled breeding efficiency; annual infant survival rates >90% under veterinary care.	Unpredictable breeding cycles; infant mortality exceeds 20%–25% from environmental stress.	Provides a predictable, resilient supply chain for multi-generational safety studies.
Estimated Cost per Subject	USD \$10,000–\$15,000+ (high initial cost due to SPF barrier maintenance and diagnostic audits).	USD \$2,000–\$4,000 (low initial cost, but high risk of mid-trial failure due to latent disease).	Mitigates mid-trial loss risks that can cost sponsors over USD \$500,000 in failed drug candidate testing.
Age & Demographic Standardization	Fully age-matched cohorts; exact date of birth, rearing history, and dietary logs known.	Heterogeneous, estimated age classes; unstandardized nutritional and exposure histories.	Eliminates age-dependent metabolic variance, improving baseline pharmacokinetic assay precision by 35%–50%.
Institutional Security	Transparent compliance with CITES Appendix II and international ethical audits.	High exposure to legal vulnerabilities, conservation lawsuits, and global public relations damage.	Safeguards the scientific standing, investments, and reputation of global research institutions.

matrices—designed to stimulate natural foraging and social behaviors (Tardif *et al.*, 2013; Sajuthi *et al.*, 2016). Refinement strategies are continuously updated to introduce non-invasive biometric monitoring – such as fecal glucocorticoid metabolite (FGM) cortisol tracking, automated infrared thermography, and passive video behavioral telemetry – while replacement advocacy drives funding toward validated in vitro tissue-chip models and high-fidelity computer simulations to systematically reduce future primate dependency (Burm, 2014).

Enforcement of these wildlife protection statutes has been significantly bolstered through joint operations by the Directorate General of Environment and Forestry Law Enforcement (GAKKUM KLHK) and the Indonesian National Police. Between 2020 and 2025, over 45 wildlife trafficking prosecutions specifically involving macaques were successfully executed under Law No. 5/1990 (Padang *et al.*, 2025; GAKKUM KLHK, 2025). This active national

enforcement mechanism penalizes non-compliance, shuts down illegal trade rings, and revokes the operational permits of substandard breeding facilities (Padang *et al.*, 2025).

From an international trade and population management perspective, *Macaca fascicularis* is strictly regulated under Appendix II of CITES, requiring comprehensive, transparent monitoring of all border crossings to ensure trade does not threaten the survival of wild populations (Sajuthi *et al.*, 2016; Kloppe, 2025). Indonesia manages this through a strict administrative workflow: the Ministry of Environment and Forestry (KLHK), acting as the Management Authority, issues the Foreign Transport Permit for Plants and Wildlife (SATS-LN) only after receiving formal scientific clearance from the National Research and Innovation Agency (BRIN), which acts as the Scientific Authority (Government of Indonesia, 1990; KLHK, 2018). Under

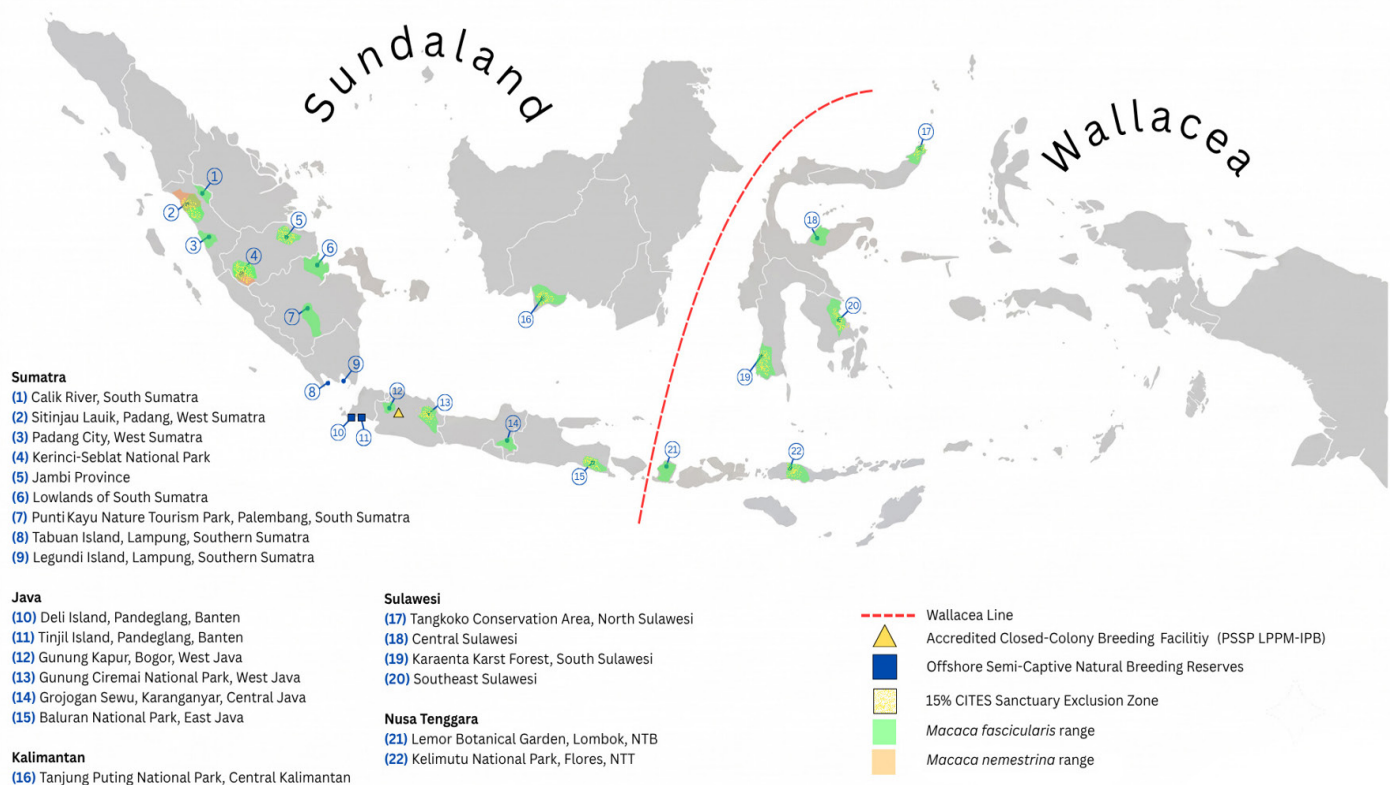


Figure 1: Biogeographical distribution, key demographic populations, and regulatory zoning of *Macaca* species across Indonesia. The map delineates the major biogeographical transition between Sundaland and Wallacea separated by the Wallace Line (dashed red curve). Colored spatial overlays represent species-specific distribution ranges mapped from regional census literature, differentiating *Macaca fascicularis* (light green) from *Macaca nemestrina* (orange) across mainland Sumatra, Java, Kalimantan, Sulawesi, and Nusa Tenggara. Hatched pattern overlays designate the mandatory 15% CITES Sanctuary Exclusion Zones (yellow dot) enforced across core protected national park boundaries. Specific wild census populations and study sites are numbered sequentially across regions (1–22): Sumatra (1–9), Java (10–15), Kalimantan (16), Sulawesi (17–20), and Nusa Tenggara (21–22). Institutional breeding hubs are highlighted using distinct geometric markers, separating accredited laboratory-based Specific Pathogen-Free (SPF) closed-colony breeding infrastructure (yellow triangle, PSSP LPPM-IPB, Bogor) from offshore semi-captive natural breeding reserves (blue squares, Deli Island and Tinjil Island, Pandeglang, Banten).

the latest 2023 NDF assessment, BRIN utilizes dynamic demographic modeling to enforce a mandatory 15% sanctuary exclusion zone across the species' natural range, entirely banning all wild extraction within these zones. This 15% spatial exclusion figure is scientifically grounded in CITES NDF source-sink population models, ensuring that pristine core habitats remain untouched to sustain regional genetic pools. Furthermore, strict age, size, and seasonal harvest restrictions are enforced to safeguard the breeding core of wild populations (BRIN and KLHK, 2023; Fitriana *et al.*, 2024).

This data-driven management architecture is vital to successfully balancing the demands of global health research with the realities of human-macaque conflicts on agricultural borders. Although long-tailed macaques maintain a broad geographical range, rapid land-use changes and deforestation drive localized populations into intense friction with rural communities; addressing these

complex socio-ecological challenges requires adaptive, community-inclusive co-management programs (Fitriana *et al.*, 2024; Nugroho *et al.*, 2025; Riyani *et al.*, 2025).

Ultimately, Indonesia's capacity to operate as a sustainable, premium hub for the global biomedical supply chain is heavily reinforced by its mature, internationally validated breeding infrastructure (Gettayacamin *et al.*, 2018). By producing standardized, multi-generational (F2+) captive-born cohorts within AAALAC-certified, closed-colony SPF environments, Indonesia satisfies the most stringent ethical and scientific criteria demanded by major global regulatory agencies and high-impact peer-reviewed journals (Sajuthi *et al.*, 2016; Gettayacamin *et al.*, 2018; KLHK, 2018). Consequently, Indonesia's regulatory framework does not merely serve as a passive conservation filter, but functions as a sophisticated legal and scientific framework that protects native genetic repositories while asserting national scientific excellence on the global stage

RECOMMENDATIONS

Operationalizing the national transition from wild harvesting toward a sustainable, premium closed-colony export paradigm requires four coordinated strategic interventions. First, to standardize national population monitoring, the Ministry of Environment and Forestry (KLHK) and the National Research and Innovation Agency (BRIN) must establish a unified census protocol that combines Spatially Explicit Capture-Recapture (SECR) line transects with non-invasive environmental DNA (eDNA) barcoding, eliminating historical methodological heterogeneities and yielding calibrated baseline data for CITES Non-Detrimental Findings (NDF) quotas. Second, to enhance Specific Pathogen-Free (SPF) breeding capacity, the Indonesian government should grant targeted fiscal incentives, tax deductions, and streamlined export permitting for research institutions investing in AAALAC-compliant, high-barrier housing, thereby scaling up second-generation (F2+) breeding cohorts to meet global demand without wild extraction. Third, regulatory enforcement must be strengthened by empowering a centralized veterinary board to standardize Institutional Animal Care and Use Committee (IACUC) training across domestic facilities, alongside intensified joint field operations between GAKKUM KLHK and the Indonesian National Police to enforce zero-tolerance anti-poaching policies. Fourth, international research collaborations should be formalized through public-private consortia enforcing Nagoya Protocol-compliant Material Transfer Agreements (MTAs) to guarantee equitable benefit-sharing, protect domestic intellectual property, and preserve national genetic sovereignty over biological specimens and Digital Sequence Information (DSI).

LIMITATIONS

While this review offers a comprehensive synthesis of the Indonesian macaque supply chain, several methodological constraints must be acknowledged. Primarily, the reliance on secondary literature spanning a broad temporal range (2009–2025) introduces analytical heterogeneity, as disparate field methodologies (e.g., direct line-transects versus spatial predictive modeling) limit direct quantitative meta-analyses across islands. Furthermore, the paucity of recent primary census data from deep-forest interiors forces regional population estimates to depend on canopy-cover extrapolation models that may not fully reflect localized, recent habitat degradation. Finally, a subtle publication bias exists within laboratory animal science literature, where failed replication attempts or trial retractions directly caused by subclinical viral reactivations are rarely formally published; consequently, quantitative estimates of non-SPF confounding effects rely predominantly on baseline

immunological variance parameters rather than published trial retraction records.

FUTURE DIRECTIONS

To resolve lingering uncertainties and advance the sustainability of non-human primate research, future scientific inquiry should prioritize three core domains. High-throughput immunogenomic mapping across wild and captive populations is urgently needed to characterize Major Histocompatibility Complex (MHC) allelic variations, establishing genomic baselines that prevent inbreeding depression in closed colonies. Concurrently, researchers should focus on developing and validating real-time, non-invasive welfare monitoring tools—such as automated infrared thermography, artificial intelligence-driven facial grimace scoring, and fecal glucocorticoid metabolite tracking—to refine stress mitigation during transport and handling. Lastly, interdisciplinary studies must evaluate how microfluidic human organ-on-a-chip systems and AI-driven pharmacokinetic models can be integrated into preclinical testing pipelines to systematically reduce reliance on live non-human primates under the Replacement mandate of the 3Rs ethos.

CONCLUSION

Indonesia is uniquely positioned to redefine the future of the global Macaca primate supply chain for international biomedical research. By aggressively transitioning away from wild-caught extraction toward internationally accredited, AAALAC-certified, and SPF closed-colony breeding platforms, the nation successfully addresses two pivotal mandates: providing the global scientific community with unparalleled, high-reproducibility animal models for advanced therapeutic development, while simultaneously ensuring the absolute ecological preservation and genetic sovereignty of its wild primate populations in strict accordance with CITES protocols and the 3Rs ethos.

Furthermore, transitioning to closed-colony breeding serves as a powerful shield for Indonesia's genetic sovereignty. By maintaining fully pedigree-tracked, captive-bred cohorts within domestic boundaries, the state ensures that valuable genetic material and unique immunological baselines are legally documented and governed under Law No. 11/2013, which fully ratified the Nagoya Protocol into Indonesian national law (Buck and Hamilton, 2011; Government of Indonesia, 2013). However, physical domestic boundaries alone cannot prevent unauthorized biological sample sharing or Digital Sequence Information (DSI) transfer; therefore, international research collaborations require rigorous administrative governance through legally binding Material Transfer Agreements (MTAs) and data-sharing protocols (Schroeder *et al.*, 2018). This active

administrative oversight prevents unauthorized biopiracy while guaranteeing fair benefit-sharing, directly advancing Indonesia's strategic bio-economy interests by shifting the national paradigm from low-margin raw animal exports toward high-value contract research partnerships, local biomedical infrastructure development, and downstream intellectual property co-ownership.

To successfully operationalize this national transition and secure Indonesia's leadership in the global bio-economy, a coordinated national roadmap is urgently required. First, the Indonesian government—specifically through joint initiatives by the Ministry of Environment and Forestry (KLHK) and the National Research and Innovation Agency (BRIN)—should establish concrete fiscal mechanisms, including multi-year corporate tax breaks for facilities building AAALAC-compliant SPF barrier housing, targeted national research grants for captive breeding innovation, and import tariff exemptions for specialized diagnostic and filtration equipment.. Second, national regulatory bodies must mandate standardized, rigorous IACUC training and certification across all domestic facilities, acknowledging that this mandate necessitates significant initial capacity-building initiatives led by national veterinary associations and academic primatology centers to harmonize welfare audits under the 3Rs principles. Lastly, establishing robust public-private partnerships with international biomedical consortia will provide the necessary venture capital to scale-up F2+ generation breeding colonies. To mitigate risks of foreign over-control, these partnerships must mandate strict state oversight, domestic co-investigation, and co-ownership of genetic data, securing Indonesia's dual position as an uncompromising protector of its native biodiversity and a sovereign, high-value leader in global translational science (Buck and Hamilton, 2011; Tian., 2021).

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NOVELTY STATEMENT

Unlike previous primate reviews that focus strictly on field ecology or laboratory protocols in isolation, this paper provides a novel, integrated synthesis of the geopolitical, regulatory, and biomedical supply chain dynamics of Indonesian *Macaca* primates. While prior literature has examined regional supply chain models in contexts such as Mauritius (Sussman *et al*, 2011), this review fills a

fundamental gap by establishing a tailored, post-2022 framework for a megadiverse origin nation navigating the IUCN Endangered reclassification of *M. fascicularis*.. By introducing a comparative analysis framework (Table 2), this review quantitatively illustrates and systematically compares how transitioning to F2+ SPF closed-colony breeding directly translates ethical 3Rs compliance into reduced baseline experimental variance and maximized statistical power. It establishes a new paradigm showing that strict ex-situ captive-breeding dynamics do not conflict with conservation, but rather serve as an active, direct mechanism to alleviate wild extraction pressures and guarantee national genetic sovereignty (Buck and Hamilton, 2011).

AUTHORS CONTRIBUTION

ZIA, BS, MM, FA, and AW conceptualized the review, defined the scope of the global *Macaca* supply chain framework, and designed the overall structure of the manuscript. ZA, NR, SA, AZ, and GAH performed the extensive literature search, extracted the regional demographic statistics, and compiled the comprehensive population density data for Table 1. SER, VO, HU, ANB, and GAH analyzed the closed-colony breeding models, evaluated the biological impact of Specific Pathogen-Free (SPF) status on experimental rigor, and structured the comparative matrix for Table 2. LRY, AZ, and HU critically reviewed the domestic legal frameworks, CITES Appendix II compliance, and the Non-Detrimental Findings (NDF) administrative pathways. ZIA, ZA, NR, SER, FA, AZ, ANB, and LRY drafted the initial sections of the manuscript. BS, SA, MM, VO, HU, GAH, FA, AZ, ANB and AW participated in technical validation, critically revised the manuscript for intellectual and veterinary medical content, and refined the academic language. AW coordinated the collaborative research group and provided final administrative oversight. All authors have read, verified, and approved the final version of this manuscript for submission.

GENERATIVE AI AND AI ASSISTED TECHNOLOGY STATEMENT

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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