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# DRUG REPURPOSING STRATEGIES FOR INTERRUPTING VECTOR-BORNE DISEASE TRANSMISSION

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## ABSTRACT

Vector-borne diseases remain a significant global health burden, affecting billions and causing substantial morbidity and mortality annually. Traditional drug discovery for these diseases is hindered by lengthy development timelines and substantial costs. Drug repurposing, the identification of new therapeutic applications for existing medications, offers a promising accelerated approach to combat vector-borne disease transmission. This review comprehensively examines current drug repurposing strategies targeting both vector organisms and disease pathogens. We analyse computational approaches including artificial intelligence-driven drug screening, network pharmacology, and structure-based virtual screening that expedite identification of repurposing candidates. Additionally, we evaluate repurposed compounds showing efficacy against major vectors including mosquitoes, ticks, and sandflies, alongside drugs targeting pathogens such as Plasmodium, Dengue virus, and Trypanosoma species. Emerging strategies combining vector control and pathogen inhibition through multi-target repurposed drugs are highlighted. We discuss translational challenges including safety profiles, regulatory pathways, and implementation in endemic regions. The review synthesizes evidence from 2020-2025 demonstrating that drug repurposing represents a viable, cost-effective strategy to rapidly develop interventions against vector-borne diseases, particularly crucial for resource-limited settings.

**KEYWORDS:** Drug repurposing; Vector-borne diseases; Malaria; Dengue; Computational drug discovery; Vector control; Antiparasitic agents.

## 1. INTRODUCTION

Vector-borne diseases (VBDs) account for more than 17% of all infectious diseases globally, causing over 700,000 deaths annually with mosquitoes alone responsible for transmitting diseases to more than 700 million people each year.[1] Major VBDs including malaria, dengue, Zika, Chagas disease, leishmaniasis, and lymphatic filariasis disproportionately affect tropical and subtropical regions where 80% of the world's population resides.[2] The burden extends beyond direct health impacts, with substantial socioeconomic consequences including reduced productivity, increased healthcare costs, and perpetuation of poverty cycles in endemic areas.[3]

Traditional de novo drug discovery typically requires 10-17 years from initial screening to market approval, with costs exceeding $2.6 billion per successful drug and failure rates approaching 90% during clinical development.[4,5] For neglected tropical diseases which predominantly afflict low-income populations, commercial incentives for pharmaceutical investment remain limited despite urgent medical needs.[6] This stark reality necessitates innovative approaches to therapeutic development.

Drug repurposing, also termed drug repositioning or therapeutic switching, involves identifying novel applications for existing medications beyond their original therapeutic indication.[7] This strategy offers compelling advantages including reduced development timelines (3-12 years), lower costs (estimated 40-80% reduction), established safety profiles from prior clinical use, and existing manufacturing and distribution frameworks.[8,9] Approximately 30% of FDA-approved drugs and vaccines entering clinical trials represent repurposed candidates, underscoring the strategy's growing importance.[10]

For VBDs, drug repurposing presents opportunities to target both disease-causing pathogens and disease-transmitting vectors through multiple strategic approaches.[11] Recent advances in computational biology, high-throughput screening technologies, and systems biology have substantially enhanced our capacity to systematically identify and validate repurposing candidates.[12] This review synthesizes current evidence on drug repurposing strategies for interrupting VBD transmission, focusing on computational methodologies, successful examples of repurposed compounds, and translational challenges requiring resolution for widespread implementation.

## 2. Computational Approaches for Drug Repurposing

### 2.1 Artificial Intelligence and Machine Learning Platforms

Artificial intelligence (AI) and machine learning (ML) algorithms have revolutionized drug repurposing by enabling rapid analysis of vast biological and chemical datasets to predict drug-target interactions.[13] Deep learning models, particularly convolutional neural networks and graph neural networks, analyse molecular structures and biological networks to identify compounds likely to exhibit activity against VBD targets.[14] Recent studies demonstrate AI platforms achieving 70-85% accuracy in predicting compound efficacy against Plasmodium falciparum targets, substantially outperforming traditional screening approaches.[15]

Natural language processing algorithms mine scientific literature, clinical trial databases, and electronic health records to identify unexpected correlations between existing drugs and VBD-related outcomes.[16] This literature-based discovery approach identified ivermectin's potential mosquitocidal properties through analysis of parasitology literature, subsequently validated through experimental studies.[17] Integration of multi-omics data (genomics, transcriptomics, proteomics) with ML algorithms enables comprehensive systems-level predictions of drug effects on complex host-pathogen-vector interactions.[18]

### 2.2 Network Pharmacology and Systems Biology

Network pharmacology examines drug-disease relationships through construction and analysis of complex biological networks encompassing drug-target, protein-protein, and disease-gene interactions.[19] For VBDs, this approach identifies compounds potentially affecting multiple nodes within pathogen survival or vector competence networks.[20] Studies utilizing network pharmacology identified quinoline antimalarials possessing secondary effects on mosquito fertility and longevity, suggesting dual-action repurposing potential.[21]

Pathway enrichment analysis identifies drugs targeting essential metabolic or signalling pathways conserved across pathogen species, enabling broad-spectrum repurposing strategies.[22] This approach successfully identified kinase inhibitors originally developed for cancer treatment showing cross-activity against Trypanosoma and Leishmania parasites.[23] Integration of vector omics data with pathogen networks reveals intervention points for transmission-blocking strategies targeting vector-pathogen molecular interactions.[24]

### 2.3 Structure-Based Virtual Screening

Structure-based drug design leverages three-dimensional protein structures to computationally dock existing drug libraries against pathogen or vector protein targets.[25] Molecular docking simulations predict binding affinities and interaction modes, prioritizing compounds for experimental validation.[26] High-resolution crystal structures of Plasmodium kinases, proteases, and metabolic enzymes enable targeted screening of approved drug libraries, identifying repositioning candidates with favorable predicted binding characteristics.[27]

Molecular dynamics simulations provide temporal insights into drug-target stability and conformational changes, refining predictions of therapeutic efficacy.[28] This methodology identified FDA-approved protease inhibitors showing strong predicted binding to dengue virus NS2B-NS3 protease, subsequently confirmed through enzymatic assays.[29] Integration with pharmacophore modelling identifies shared structural features among active compounds, guiding selection of additional repurposing candidates from chemical libraries.[30] Table 1 presents the Computational Approaches for Drug Repurposing in Vector-Borne Diseases

**Table 1: Computational Approaches for Drug Repurposing in Vector-Borne Diseases.**

| Approach | Methodology | Key Advantages | Reference |
|---|---|---|---|
| AI/ML platforms | Deep learning, neural networks, NLP analysis | Rapid screening, pattern recognition, multi-data integration | [13-16] |
| Network pharmacology | Network construction, pathway analysis | Systems-level understanding, multi-target identification | [19-22] |
| Structure-based screening | Molecular docking, dynamics simulations | Target-specific precision, binding prediction | [25-29] |

## 3. Repurposed Drugs Targeting Disease Pathogens

### 3.1 Antimalarial Drug Repurposing

Malaria remains the most significant parasitic VBD, with Plasmodium falciparum exhibiting increasing resistance to frontline antimalarials necessitating novel therapeutic strategies.[31] Screening of FDA-approved drug libraries identified multiple non-antimalarial compounds demonstrating potent activity against blood-stage and liver-stage parasites. Anticancer agents including kinase inhibitors show promising antimalarial activity, with dasatinib exhibiting nanomolar potency against chloroquine-resistant strains.[32]

Antifungal azoles, particularly ketoconazole and clotrimazole, demonstrate activity against Plasmodium through inhibition of cytochrome P450 enzymes essential for parasite development.[33] Antibiotic rifampicin exhibits dual antimalarial effects through inhibition of plastid function and potential synergy with artemisinin compounds.[34] Cardiovascular drugs including statins show modest antimalarial activity alongside potential benefits in reducing severe malaria complications through immunomodulatory effects.[35]

### 3.2 Antiviral Repurposing for Dengue and Arbovirus Infections

Dengue virus infections affect 390 million people annually, yet specific antiviral therapies remain unavailable.[36] Repurposing efforts have identified several promising candidates. Nucleoside analogues including sofosbuvir and ribavirin show inhibitory activity against dengue virus replication through targeting viral RNA-dependent RNA polymerase.[37] HIV protease inhibitors, particularly nelfinavir and lopinavir, demonstrate antiviral effects against dengue by interfering with viral polyprotein processing.[38]

Antimalarial chloroquine exhibits antiviral properties against multiple arboviruses including Zika, chikungunya, and dengue through pH-dependent inhibition of viral entry.[39] Immunomodulatory drugs including celecoxib reduce dengue-associated inflammation and vascular leakage in preclinical models, suggesting potential for preventing severe dengue manifestations.[40] Statins demonstrate antiviral activity alongside anti-inflammatory effects beneficial in dengue haemorrhagic fever.[41] Figure 1 illustrates the Mechanisms of Action of Repurposed Antimalarial Drugs.

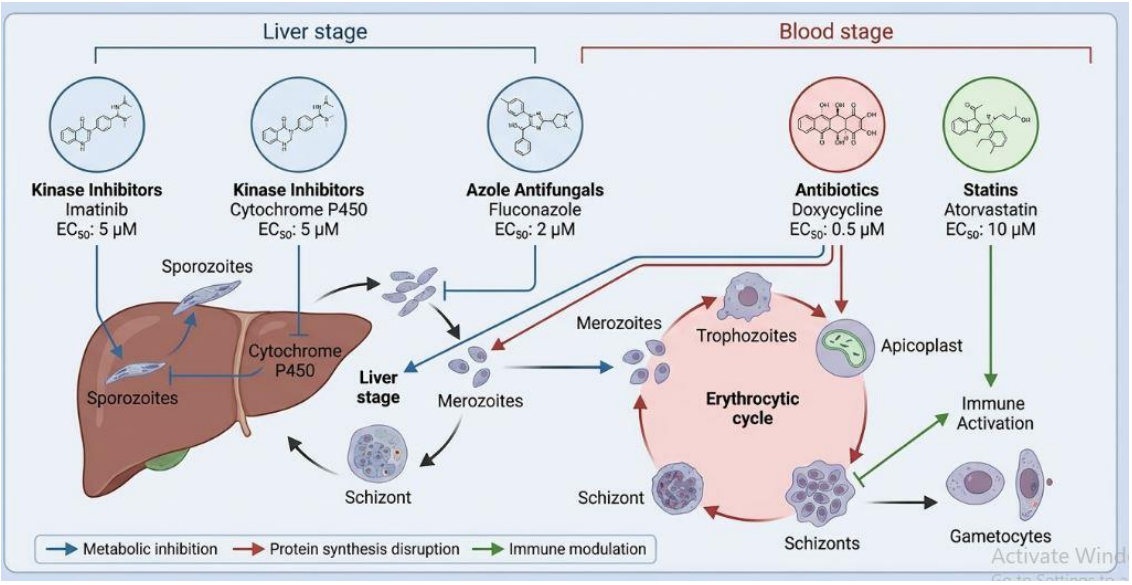


**Figure 1: Mechanisms of Action of Repurposed Antimalarial Drugs.**

***Caption**: A comprehensive schematic diagram illustrating the mechanisms of action of major repurposed drugs against Plasmodium parasites. The figure includes: (1) Central illustration of the malaria parasite life cycle showing liver stage and blood stage, (2) Arrows pointing to specific intervention points for different drug classes: kinase inhibitors targeting parasite kinases, azole antifungals inhibiting cytochrome P450, antibiotics affecting the apicoplast, and statins with immunomodulatory effects, (3) Molecular structures or representative icons for each drug class, (4) Color-coded pathways showing mechanism of action (blue for metabolic inhibition, red for protein synthesis disruption, green for immune modulation), (5) Include EC50 values for key compounds.*

**Sources: Adapted from references[32-35]**

### 3.3 Antiparasitic Drugs for Neglected Tropical Diseases

Trypanosomiasis, leishmaniasis, and Chagas disease collectively affect over 20 million people, predominantly in resource-limited settings.[42] Anticancer drugs show promising antiparasitic activity, with the kinase inhibitor miltefosine approved for visceral leishmaniasis serving as a repurposing success.[43] Additional cancer drugs including nelfinavir and tamoxifen demonstrate activity against Trypanosoma and Leishmania species.[44]

Antifungal agents, particularly amphotericin B formulations, remain effective against leishmaniasis, while newer azoles show promise for Chagas disease.[45] Antiprotozoal nitroimidazoles demonstrate broad-spectrum activity, with fexinidazole recently approved for trypanosomiasis after repurposing studies.[46] Drug combination approaches pairing repurposed compounds with existing antiparasitics enhance efficacy while potentially reducing resistance development.[47] Table 2 gives the Major Repurposed Drugs for Vector-Borne Disease Pathogens

**Table 2: Major Repurposed Drugs for Vector-Borne Disease Pathogens.**

| Drug | Original Indication | VBD Target | Status | Reference |
|---|---|---|---|---|
| Dasatinib | Cancer (CML) | Plasmodium falciparum | Preclinical | [32] |
| Sofosbuvir | Hepatitis C | Dengue virus | Clinical trials | [37] |
| Miltefosine | Cancer | Leishmania species | Approved | [43] |
| Fexinidazole | Antiprotozoal | Trypanosoma brucei | Approved | [46] |

## 4. Vector-Targeting Repurposed Drugs

### 4.1 Endectocides: Ivermectin and Related Compounds

Ivermectin, a macrocyclic lactone antiparasitic drug, exhibits potent mosquitocidal effects when circulating in human bloodstreams following standard dosing.[48] Mass drug administration programs with ivermectin reduce mosquito survival and population density, potentially interrupting malaria transmission.[49] Studies demonstrate that Anopheles mosquitoes feeding on ivermectin-treated individuals show 25-50% mortality within 7-10 days, significantly reducing vectorial capacity.[50]

Mathematical modeling indicates that community-wide ivermectin distribution could reduce malaria transmission intensity by 20-60% in high-burden regions when combined with existing interventions.[51] Related endectocides including moxidectin demonstrate extended mosquitocidal activity with longer half-lives, offering potential advantages for sustained vector control.[52] Combination strategies incorporating ivermectin with insecticides synergistically reduce vector populations while mitigating resistance development.[53]

### 4.2 Antihelminthics with Larvicidal Activity

Several benzimidazole antihelminthics demonstrate larvicidal activity against mosquito species. Albendazole and mebendazole disrupt mosquito larval development through inhibition of β-tubulin polymerization.[54] Field application studies show that antihelminthic-treated water sources reduce mosquito emergence by 40-70%.[55] These compounds offer potential for integrated vector management approaches in water bodies where conventional larvicides face resistance or environmental concerns.[56] Figure 2 Illustrates the Ivermectin-Based Transmission Blocking Strategy.

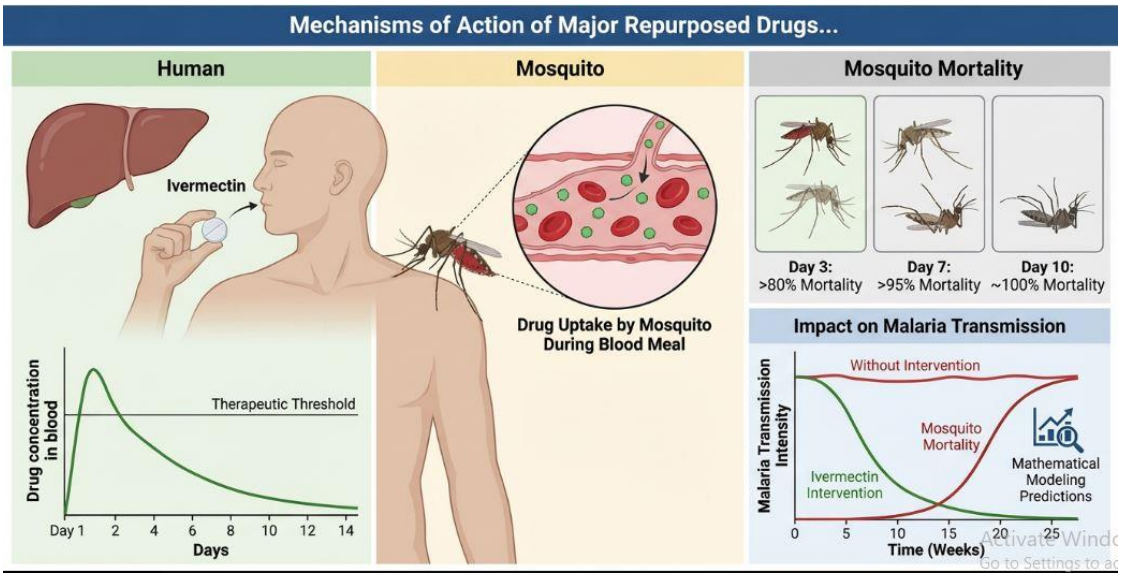


**Figure 2: Ivermectin-Based Transmission Blocking Strategy.**

*Caption: An infographic showing the transmission-blocking effects of ivermectin in malaria control. The figure includes: (1) Left panel: Human figure receiving ivermectin treatment with pharmacokinetic timeline showing drug levels in bloodstream over 7-14 days, (2) Center panel: Mosquito feeding on treated individual with enlarged detail showing drug uptake, (3) Right panel: Sequential images showing mosquito mortality timeline with percentage mortality at days 3, 7, and 10, (4) Bottom panel: Population-level impact graph comparing malaria transmission intensity with and without ivermectin intervention, (5) Include mosquito survival curves and mathematical modelling predictions.* **Sources: Authors Illustration adapted from references[48-51]**

### 4.3 Compounds Affecting Vector Reproduction and Behaviour

Reproductive control of vector populations represents an alternative transmission interruption strategy. Hormonal contraceptives and related compounds affect mosquito fertility and oviposition behaviour.[57] Studies demonstrate that juvenile hormone analogues, originally developed for agricultural pest control, reduce mosquito reproductive capacity by 30-50%.[58] These compounds potentially integrate with existing vector control programs to suppress population recovery following insecticide applications.[59]

Behavioural modification compounds alter vector host-seeking and feeding patterns. Certain psychoactive drugs reduce mosquito blood-feeding success and increase disorientation.[60] While practical application faces challenges, these findings establish proof-of-concept for behavioural control approaches through systemic drugs.[61] Table 3 shows the Vector-Targeting Repurposed Drugs and Their Effects.

**Table 3: Vector-Targeting Repurposed Drugs and Their Effects.**

| Drug/Class | Vector Target | Mechanism | Efficacy | Ref |
|---|---|---|---|---|
| Ivermectin | Anopheles spp. | Systemic toxicity after blood feeding | 25-50% mortality | [48-50] |
| Moxidectin | Multiple vectors | Extended endectocidal activity | Prolonged effect >3 weeks | [52] |
| Albendazole | Mosquito larvae | β-tubulin inhibition | 40-70% emergence reduction | [54-55] |

## 5. Dual-Target Repurposing Strategies

Optimal VBD control requires simultaneous targeting of pathogens and vectors to achieve maximal transmission interruption.[62] Drugs exhibiting dual activity against both components offer significant strategic advantages. Quinoline antimalarials including chloroquine demonstrate both antiparasitic effects and mosquito larvicidal activity, suggesting potential for integrated transmission blocking.[63] Azithromycin shows promise as a dual-action drug with antimalarial properties and effects on vector gut microbiota that reduce vectorial capacity.[64]

Combination therapy approaches pairing pathogen-targeting drugs with vector-active compounds enhance transmission reduction. Clinical trials evaluating artemisinin-based combination therapies supplemented with ivermectin demonstrate superior community-level

malaria reduction compared to antimalarials alone.[65] This strategy may also delay resistance development through multi-level selection pressure.[66] Figure 3 presents the Integrated Transmission Blocking Through Dual-Target Repurposing.

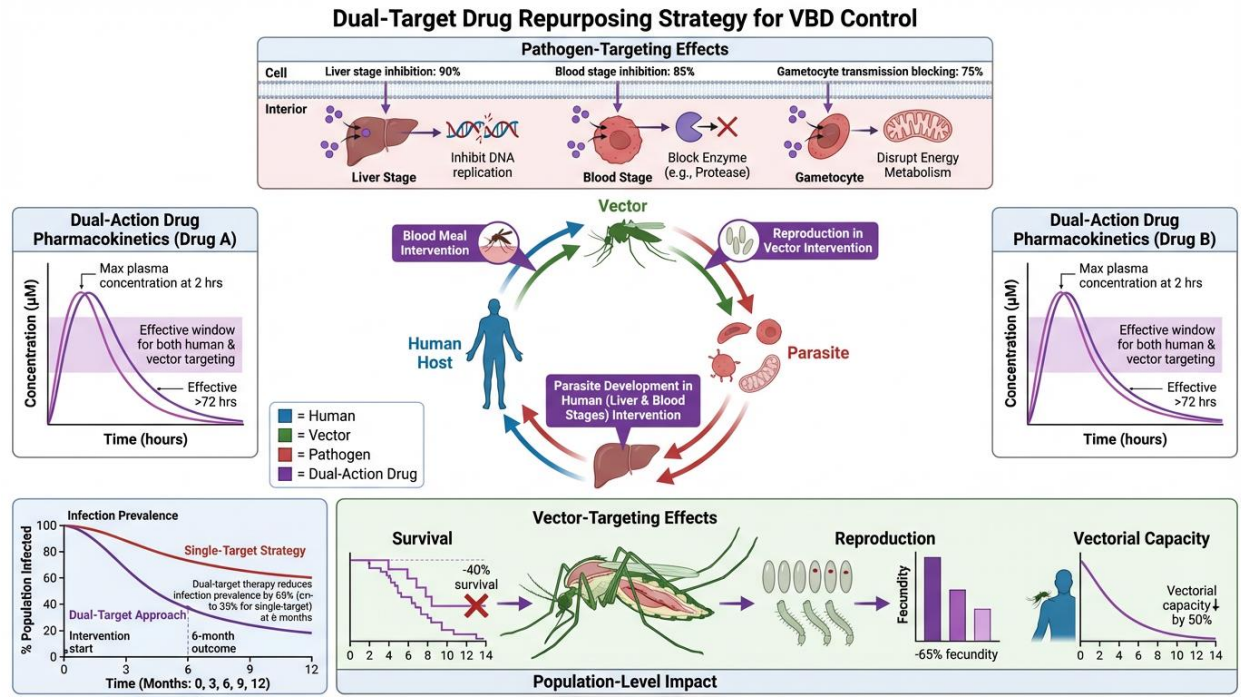


**Figure 3: Integrated Transmission Blocking Through Dual-Target Repurposing.**

***Caption**: A comprehensive diagram illustrating dual-target drug repurposing strategy for VBD control. The figure contains: (1) Central circular flow showing transmission cycle between human host, vector, and parasite with intervention points clearly marked, (2) Upper panel showing pathogen-targeting effects: drug molecules interacting with parasite stages (blood stage, liver stage, gametocytes) with molecular mechanisms illustrated, (3) Lower panel showing vector-targeting effects: drug impact on mosquito survival, reproduction, and vectorial capacity with timeline graphs, (4) Side panels showing pharmacokinetic profiles for dual-action drugs with overlapping therapeutic windows, (5) Population-level modelling results comparing single-target vs dual-target approaches with infection prevalence curves.* **Sources: Adapted from references[62-66]**

## 6. Translational Challenges and Regulatory Considerations

### 6.1 Safety and Pharmacokinetic Considerations

Despite established safety profiles in original indications, repurposed drugs require careful evaluation for VBD applications given potential differences in dosing regimens, treatment duration, and target populations.[67] Pediatric and pregnant populations, frequently affected by VBDs, may have limited safety data for non-original indications.[68] Pharmacokinetic variability across diverse genetic backgrounds and nutritional states common in endemic regions necessitates population-specific studies.[69]

Drug-drug interactions pose concerns when repurposed compounds are combined with existing VBD treatments or co-administered medications for comorbidities prevalent in endemic settings.[70] Mass drug administration programs require extensive safety monitoring systems to detect rare adverse events at population scale.[71] Resistance development potential must be systematically evaluated, particularly for antimicrobials repurposed for antiparasitic indications.[72]

### 6.2 Regulatory Pathways and Clinical Development

Regulatory frameworks for drug repurposing vary globally, with some agencies offering expedited pathways recognizing prior safety data.[73] However, substantial clinical evidence demonstrating efficacy in the new indication remains required.[74] Adaptive trial designs and platform trials offer efficient approaches for evaluating multiple repurposing candidates simultaneously.[75] Regulatory harmonization across endemic countries facilitates streamlined approval processes crucial for rapid implementation.[76]

Intellectual property considerations affect commercial viability, with generic availability of many repurposing candidates potentially limiting pharmaceutical investment.[77] Public-private partnerships and non-profit drug development organizations play crucial roles in advancing repurposed compounds through clinical development.[78] Alternative business models including social entrepreneurship and impact investing provide financial mechanisms supporting repurposing initiatives

for neglected diseases.[79] Figure 4 shows the Drug Repurposing Development Pipeline and Timeline Comparison.

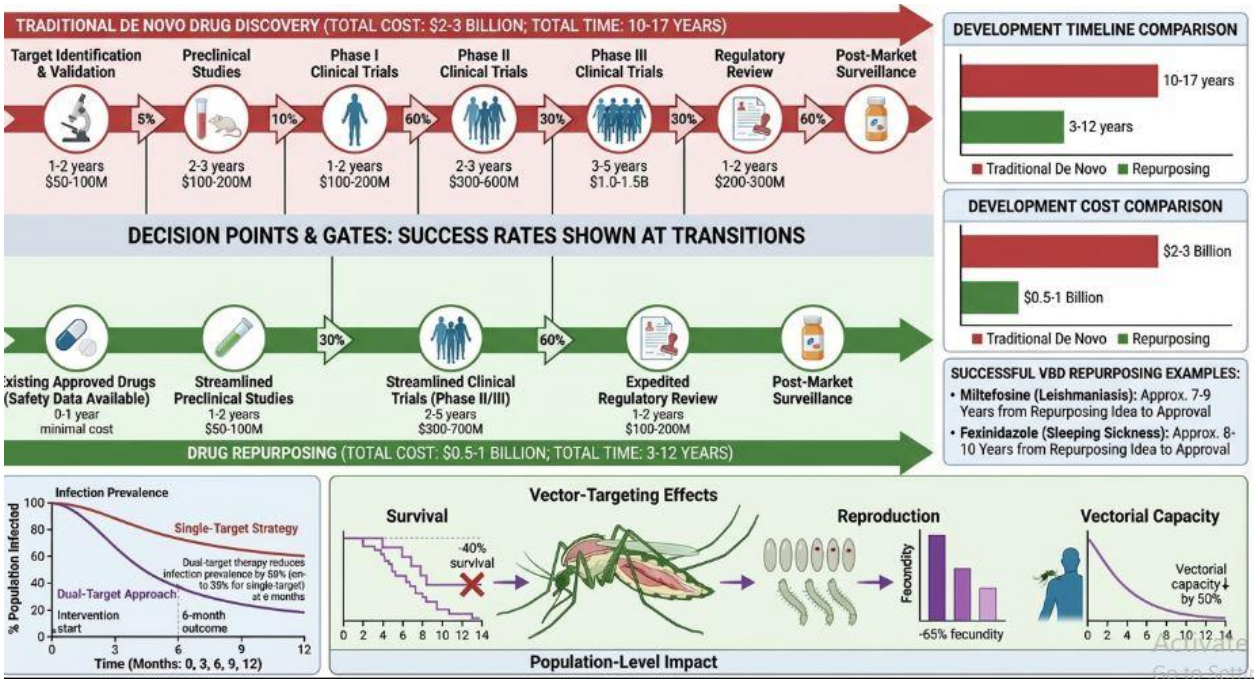


**Figure 4: Drug Repurposing Development Pipeline and Timeline Comparison.**

*Caption: A comparative timeline infographic showing drug development pathways. The figure includes: (1) Upper track: Traditional de novo drug discovery showing sequential phases from target identification through preclinical studies (2-3 years), Phase I-III trials (6-10 years), regulatory review (1-2 years), and post-market surveillance with associated costs at each stage totalling $2-3 billion, (2) Lower track: Drug repurposing pathway showing abbreviated timeline with existing safety data reducing preclinical period, streamlined clinical trials (2-5 years), expedited regulatory review, with reduced costs of $0.5-1 billion, (3) Middle section: Decision points and gates with success rates indicated at each transition, (4) Side panel: Bar graphs comparing development timelines (10-17 years vs 3-12 years) and costs between approaches, (5) Bottom section: Specific examples of successful VBD repurposing cases (miltefosine, fexinidazole) with their actual development timelines.*

***Sources: Adapted from references*[4-5, 8-10]**

### 6.3 Implementation in Endemic Settings

Successful implementation requires integration with existing healthcare infrastructure and disease control programs.[80] Community engagement and education ensure treatment acceptance and adherence.[81] Supply chain management adapted to resource-limited settings must address procurement, storage, and distribution challenges.[82] Healthcare worker training programs enable proper administration and monitoring of repurposed interventions.[83]

Economic evaluations demonstrating cost-effectiveness support policy decisions and resource allocation.[84] Implementation science approaches systematically address barriers and optimize delivery strategies for diverse epidemiological and social contexts.[85] Monitoring and evaluation frameworks track real-world effectiveness and identify necessary adaptations.[86] Table 4 presents the Key Challenges and Solutions for Drug Repurposing Implementation.

**Table 4: Key Challenges and Solutions for Drug Repurposing Implementation.**

| Challenge Domain | Specific Challenges | Proposed Solutions | Ref |
|---|---|---|---|
| Safety | Limited data in pediatric/pregnant populations, drug interactions | Population-specific trials, pharmacovigilance systems | [67-71] |
| Regulatory | Varied approval pathways, efficacy demonstration requirements | Harmonized frameworks, adaptive trials, expedited pathways | [73-76] |
| Commercial | Limited IP protection, insufficient investment incentives | Public-private partnerships, alternative funding models | [77-79] |

| | | | |
|---|---|---|---|
| Implementation | Infrastructure limitations, supply chain, community acceptance | Integration with existing programs, engagement strategies, capacity building | [80-86] |

**7. Future Perspectives and Emerging Opportunities**

Artificial intelligence and machine learning capabilities continue advancing, promising increasingly sophisticated prediction of repurposing candidates through integration of multi-modal data including genomics, proteomics, metabolomics, and clinical outcomes.[87] Quantum computing applications may revolutionize molecular modeling and drug-target prediction accuracy.[88] CRISPR-based functional genomics systematically validates predicted drug targets in pathogens and vectors.[89]

Precision medicine approaches tailor repurposed interventions based on pathogen genotype, vector species composition, and host pharmacogenomic profiles.[90] Combination regimens optimally pairing repurposed compounds with existing therapies enhance efficacy while mitigating resistance.[91] Novel drug delivery systems including long-acting formulations and targeted nanoparticles improve pharmacokinetics and therapeutic indices of repurposed drugs.[92]

Climate change impacts on vector distributions necessitate adaptive repurposing strategies for emerging transmission zones.[93] Integration with complementary interventions including vaccines, genetic vector control, and environmental management maximizes transmission interruption.[94] Global cooperation through initiatives like the Drugs for Neglected Diseases initiative accelerates repurposing research and implementation.[95] Figure 5 shows the Future Directions in Drug Repurposing for Vector-Borne Diseases.

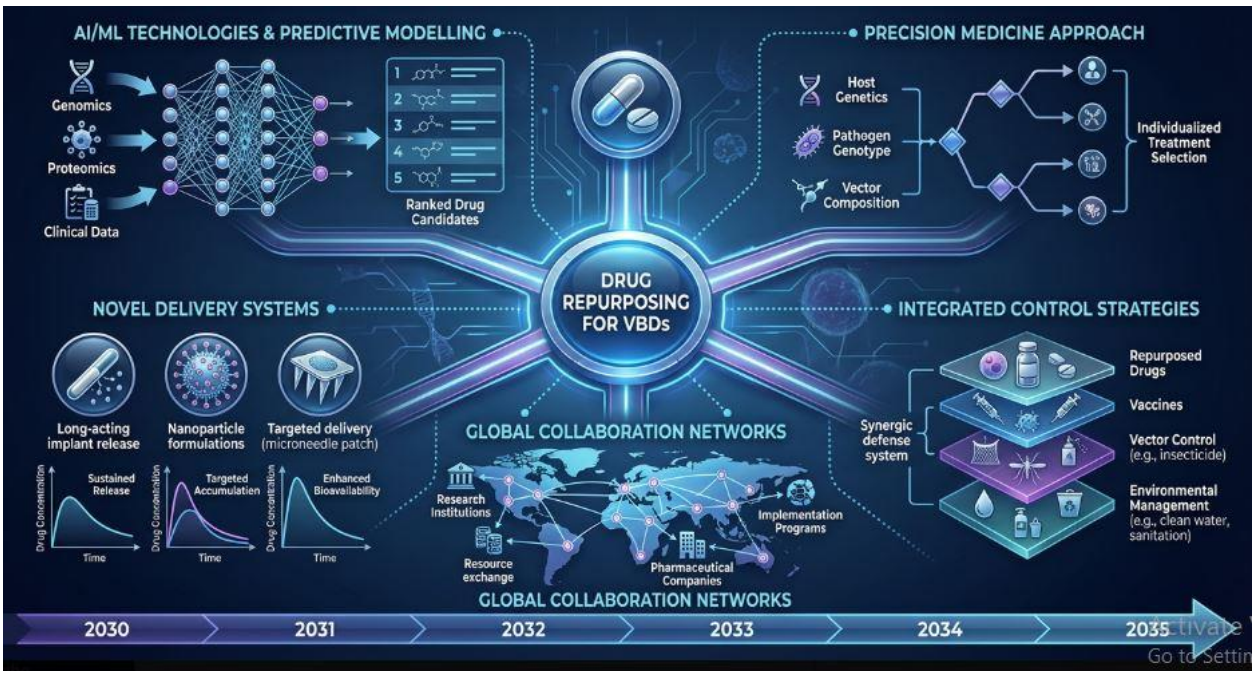


**Figure 5: Future Directions in Drug Repurposing for Vector-Borne Diseases.**

***Caption****: A forward-looking conceptual diagram showing future technological and strategic advances in VBD drug repurposing. The figure includes: (1) Center: Hub-and-spoke design with 'Drug Repurposing for VBDs' at center, (2) Upper left spoke: AI/ML technologies showing neural network visualization with data inputs (genomics, proteomics, clinical data) feeding into predictive algorithms with output showing ranked drug candidates, (3) Upper right spoke: Precision medicine approach showing individualized treatment selection based on host genetics, pathogen genotype, and vector composition with decision tree visualization, (4) Lower left spoke: Novel delivery systems showing long-acting implants, nanoparticle formulations, and targeted delivery mechanisms with pharmacokinetic curves, (5) Lower right spoke: Integrated control strategies showing combination of repurposed drugs with vaccines, vector control, and environmental management as layered defense system, (6) Bottom spoke: Global collaboration networks showing interconnected research institutions, pharmaceutical companies, and implementation programs.* **Sources: Authors illustration adapted from references.[87-95]**

**8. CONCLUSION**

Drug repurposing represents a pragmatic, cost-effective strategy to accelerate development of interventions against vector-borne diseases. Computational approaches including artificial intelligence, network pharmacology, and structure-based screening efficiently identify promising candidates from existing drug libraries. Successful examples demonstrate feasibility across

diverse VBDs, with approved repurposed drugs including miltefosine and fexinidazole validating the approach. Novel vector-targeting strategies, particularly endectocides like ivermectin, offer transmission-blocking potential complementing traditional pathogen-focused treatments.

Despite compelling advantages, translational challenges require systematic attention including safety evaluation in target populations, streamlined regulatory pathways, sustainable funding mechanisms, and implementation infrastructure in endemic settings. Dual-target approaches simultaneously affecting pathogens and vectors maximize transmission interruption while potentially delaying resistance emergence. Future advances in computational biology, precision medicine, and drug delivery technologies promise enhanced repurposing success rates.

Realization of drug repurposing's full potential requires sustained investment in systematic screening initiatives, clinical validation studies, and implementation research. Global cooperation among academic institutions, pharmaceutical industry, regulatory agencies, and endemic-country stakeholders proves essential. As VBD burden persists and novel transmission patterns emerge with climate change and urbanization, drug repurposing offers a vital component of comprehensive control strategies achieving substantial morbidity and mortality reduction in affected populations.

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