

An ecotoxicological view on malaria vector control with ivermectin-treated cattle

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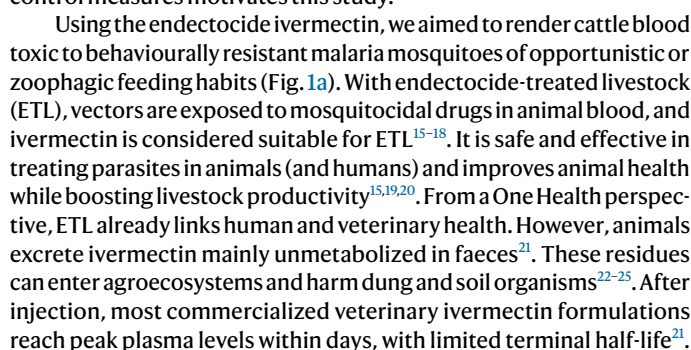
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Malaria remains an enduring challenge in sub-Saharan Africa, affecting public health and development. Control measures can include the use of insecticides that target adult *Anopheles* mosquitoes transmitting the malaria-causing *Plasmodium* parasite. Such mosquitoes can also bite livestock, allowing vector populations to be maintained at levels that enable parasite transmission. Thus, one way to control the spread of malaria includes the use of endectocide-treated livestock which renders the blood of cattle toxic to such mosquito populations. Here we present an ecotoxicological perspective on malaria vector control, using cattle treated with the endectocide ivermectin to target zoophagic and opportunistic *Anopheles coluzzii* mosquitoes. Our study employs an innovative, long-acting injectable ivermectin formulation with over 6 months of sustained mosquitocidal activity. Robust vector population modelling underscores its promising field effectiveness. Environmental implications (soil sorption and dissipation) of excreted ivermectin and potential ecotoxicological risks to non-target dung organisms in West Africa are discussed, in addition to actionable, locally inspired risk mitigation measures to protect sub-Saharan soils and agroecosystems from chemical pollution. We highlight how ecotoxicology and environmental chemistry improve livestock-based vector control with ivermectin for effective and more sustainable malaria management.

In 1962, Rachel Carson's 'Silent Spring' revealed the ecological costs of DDT, an insecticide that had previously revolutionized agriculture and malaria control^{1–3}. Carson's revelations marked a pivotal moment in environmentalism, highlighting the necessary balance

between immediate benefits and potential long-term ecological implications. This awakening paved the way for the holistic strategy called 'One Health'—an interdisciplinary, multisectoral approach that 'aims to sustainably balance and optimize the health of people,

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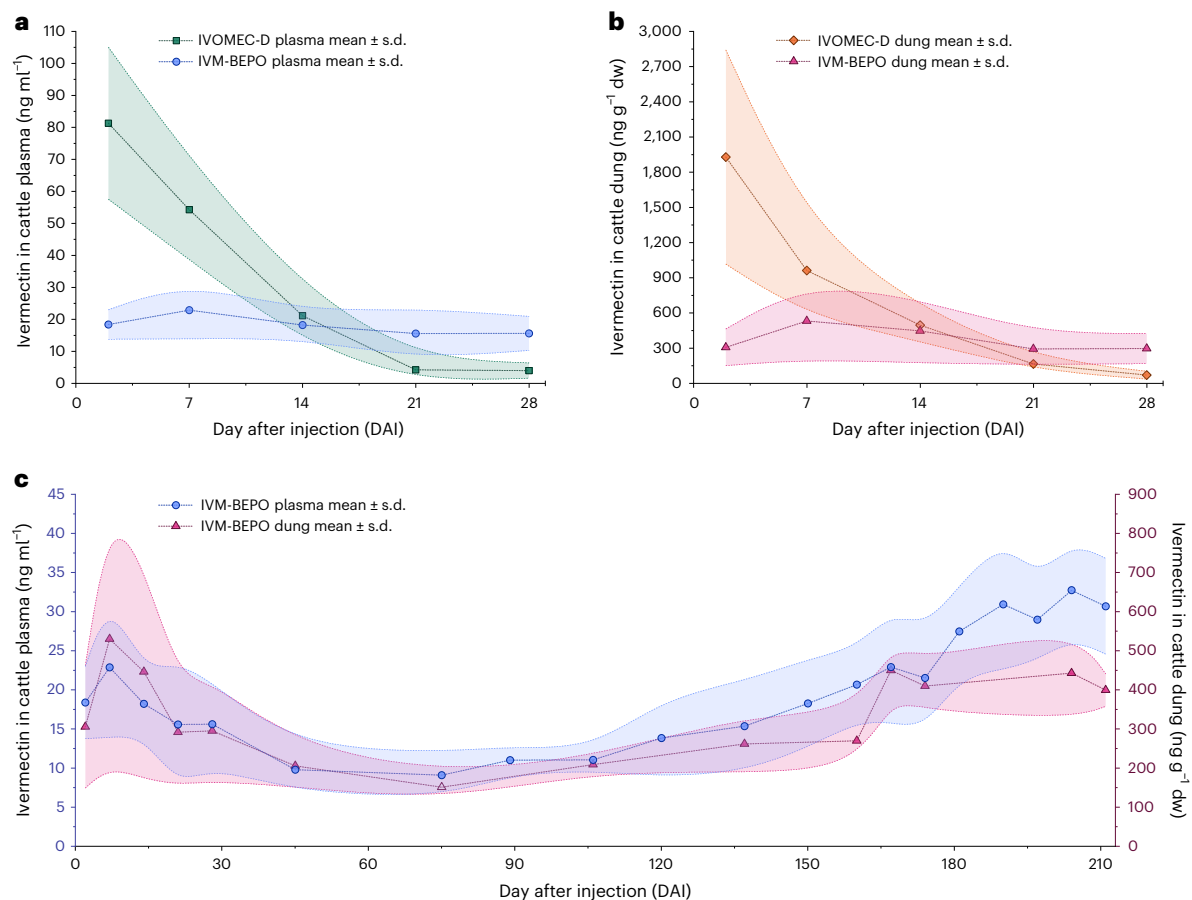


Fig. 2 | Pharmacokinetic profiles of ivermectin in cattle plasma and dung. **a,b**, Arithmetic mean $\pm$ s.d. ivermectin concentrations over 2–28 days in cattle plasma (**a**) and cattle dung (**b**) after one subcutaneous injection of a commercial (0.4 mg kg^{-1} , IVOMEC-D) or a long-acting (2.4 mg kg^{-1} , IVM-BEPO) ivermectin formulation. On DAI 21 and 28, several IVOMEC-D concentrations were below

the limit of quantification in plasma (Supplementary Table 1). **c**, Continuation of IVM-BEPO arithmetic mean $\pm$ s.d. ivermectin concentrations over 2–211 DAI in cattle plasma and dung. All points display quantifiable concentrations. **a–c**, Error bar areas show the smoothed (B-spline) s.d. of 4–8 measured samples from 2–4 treated cattle. The y axes in **c** use different scales.

These formulations provide mosquitocidal protection for approximately 2 weeks, fostering the popularity of long-acting formulations to fully cover malaria transmission seasons^{16,26,27}. However, long-acting endectocide formulations can also prolong release via cattle dung, with longer-lasting risks to non-target fauna²⁸.

We investigated cattle and *Anopheles coluzzii* mosquitoes from Burkina Faso and compared a commercialized injectable ivermectin veterinary formulation and a long-acting depot formulation, repurposed to control vectors for at least 6 months. First, we characterized pharmacokinetic profiles in cattle plasma and dung. Second, we assessed mosquitocidal efficacy through direct skin-feeding assays on cattle (Fig. 1b). Modelling approaches were used to predict field effectiveness. Third, considering environmental risks, we monitored ivermectin dissipation in dung and performed soil sorption studies with soils from Burkina Faso. We related measured dung concentrations to published ecotoxicological observations on dung organisms and propose risk mitigation measures.

While ivermectin-based strategies promise notable advantages in malaria vector control and potential benefits against other arthropod-borne zoonotic diseases, these must be balanced with environmental implications. Considering these dual perspectives, we promote a holistic view of ivermectin administration to sustainably harness its potential.

Empowered by an extensive dataset, our vector population model underscores the transformative potential of ivermectin-treated cattle and long-acting ivermectin formulations. By bridging cutting-edge vector control with ecotoxicological insight, our research aligns with

a comprehensive vision that encompasses animal health, community well-being and ecosystem preservation, reflecting the integrated, unifying approach⁴ necessary for sustainable development.

Results

Ivermectin pharmacokinetics in cattle plasma and dung

Mean ivermectin concentrations in cattle plasma and dung are shown in Fig. 2. After a single injection with the commercial IVOMEC-D formulation (not long-acting), ivermectin was detected in plasma and dung for up to 28 days (Fig. 2a,b). In plasma from the long-acting IVM-BEPO-treated cattle, ivermectin levels exceeded the limit of quantification for at least 211 days, our study duration (Fig. 2c). All control samples before and during treatment were free of detectable ivermectin. Peak mean $\pm$ s.d. concentrations for IVOMEC-D cattle were $122 \pm 35 \text{ ng ml}^{-1}$ in plasma (DAI (day after injection) 7 after the sixth injection, 160 days after study start) and $1,927 \pm 912 \text{ ng g}^{-1}$ dry weight (dw) in dung on DAI 2 after the first injection. After treatment with the long-acting formulation, maximum mean plasma concentration in the first month was documented on DAI 7 ($22.9 \pm 8.9 \text{ ng ml}^{-1}$) and, overall, on DAI 204 ($32.7 \pm 6.2 \text{ ng ml}^{-1}$). The highest mean concentrations in dung throughout the study were measured on DAI 7 ($530 \pm 327 \text{ ng g}^{-1}$ dw) after depot injection. The $C_{\text{max}}/\text{dose}$ index for plasma and dung is considerably lower for IVM-BEPO since the injected dose was six times higher compared with IVOMEC-D. Individual data points, sample sizes and pharmacokinetic parameters for ivermectin in cattle plasma and dung are summarized in Supplementary Tables 1–3.

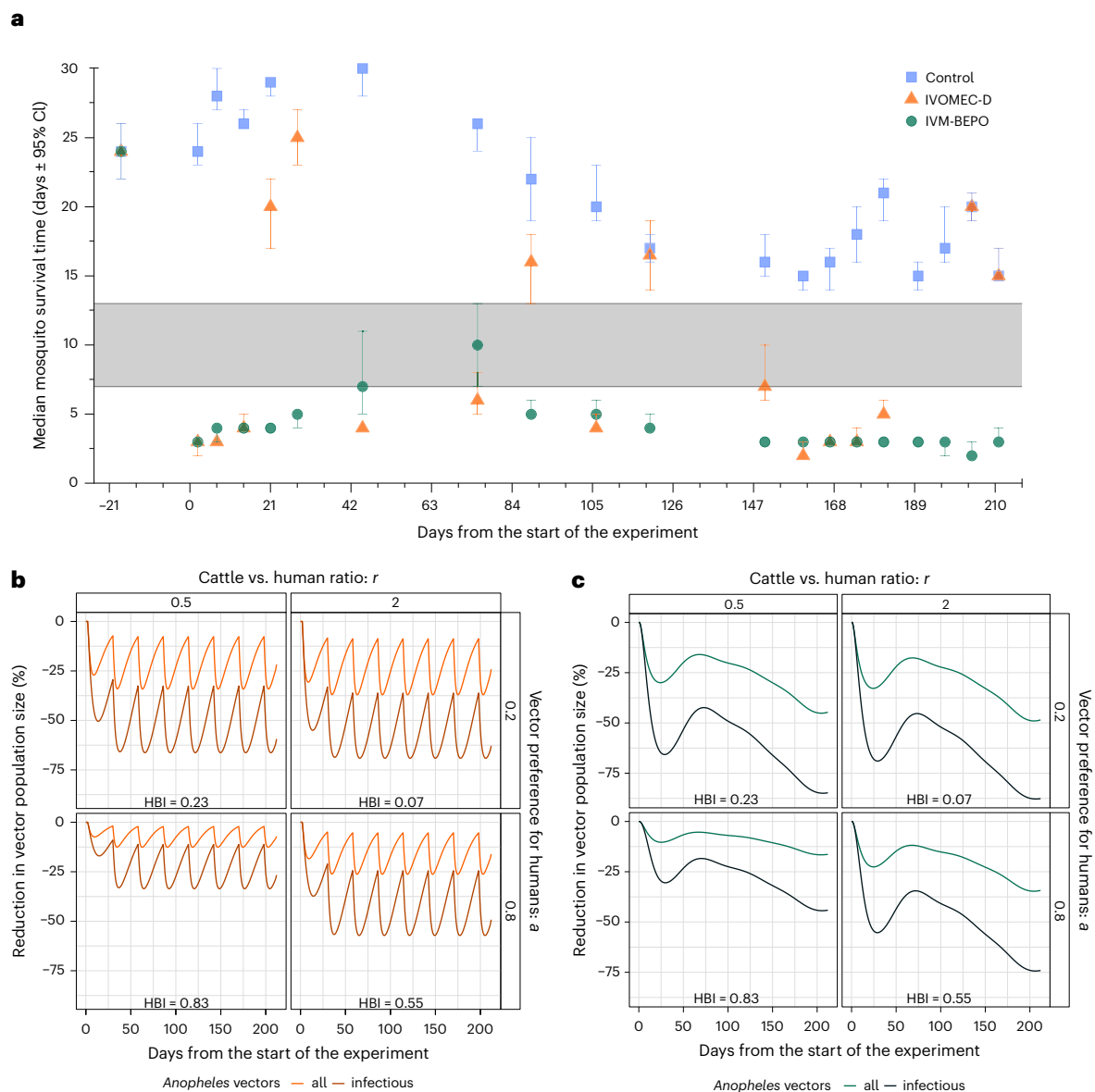


Fig. 3 | Efficacy endpoints of the ivermectin treatments measured experimentally through mosquito survival and simulated in silico using a population model. a, Median survival times $\pm$ 95% CI of mosquitoes after feeding on cattle (total $n = 5,384, 4,852$ and $5,400$ female mosquitoes, blood-fed on control, IVOMEC-D and IVM-BEPO cattle, respectively; mean $\pm$ s.d. mosquitoes per respective sampling date: $269 \pm 21.7, 269 \pm 19.4, 270 \pm 20.7$). The shaded area represents median survival times mosquitoes should reach after feeding to become infectious. *Plasmodium* extrinsic incubation period is considered 10 days, gonotrophic cycle 3 days²⁹. Survival time range encompasses two scenarios where mosquitoes feed on treated cattle 3 days before or after an infectious blood meal²⁷. Because of high survival of control mosquitoes at 21 and 45 days after the experiment started, reliable upper confidence intervals

could not be computed. **b,c**, Model prediction of IVOMEC-D (**b**) and IVM-BEPO (**c**) formulation relative effects on mosquito field population densities after mass treatment of cattle. Treatments were simulated as in this study: $0.4 \text{ mg kg}^{-1} \text{ bw}$ monthly (**b**) or on a single dose of $2.4 \text{ mg kg}^{-1} \text{ bw}$ (**c**). Different parameters were given arbitrary values to simulate treatment efficacy in different scenarios: r = cattle versus human ratio; a = vector preference for humans as measured in choice test experiments; LLIN coverage = 0.5; HBI = calculated index representing the number of mosquitoes that have taken a blood meal on humans considering all other parameters. HBI values are for an LLIN coverage index of 0.5. Refined modelling scenarios are shown in the Supplementary Information Modelling chapter.

Mosquitocidal activity

Overall, 26,637 adult female mosquitoes were allowed to blood-feed on cattle in different experimental arms, 94% of which successfully fed, without differences between arms (Wald $\chi^2 = 1.70, P = 0.42$; Supplementary Fig. 1). For survival measurements, we followed 5,384, 4,852 and 5,400 females blood-fed on control, IVOMEC-D and IVM-BEPO cattle, respectively. Mosquitoes fed on IVM-BEPO cattle always had higher mortality probabilities than control mosquitoes (all hazard ratios > 1 ; $P < 0.001$; Supplementary Table 4). IVOMEC-D-fed mosquitoes repeatedly showed similar mortality probabilities to the control (hazard ratio

not significantly different from 1 on DAI 120, 204, 211). Mosquitoes fed on IVM-BEPO-treated cattle rarely survived beyond 10 days (Fig. 3a), the median extrinsic developmental period for *Plasmodium falciparum* in field mosquitoes²⁹. With this treatment, only mosquitoes that ingested *Plasmodium* before ivermectin exposure could become infectious, transmitting parasites during only 1–3 gonotrophic cycles. However, monthly IVOMEC-D treatments often resulted in mosquito survival over 10 days, failing to block transmission. Ivermectin concentrations killing 50% of mosquitoes after 10 days were equal between formulations (IVOMEC-D $\text{LC}_{50} \pm \text{s.e.}$: $7.5 \pm 0.7 \text{ ng ml}^{-1}$; IVM-BEPO LC_{50} : $8.3 \pm 0.3 \text{ ng ml}^{-1}$;

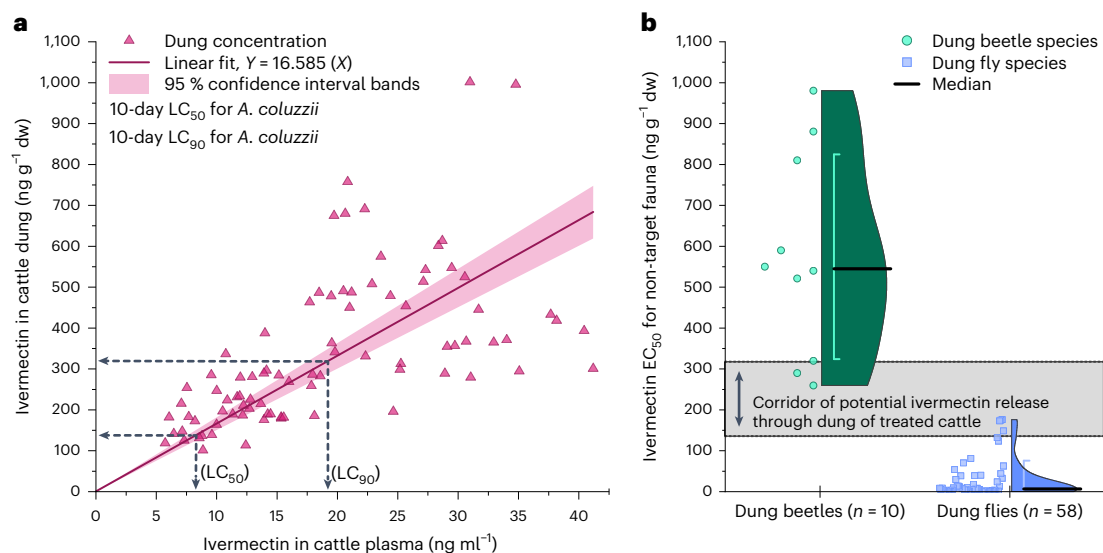


Fig. 4 | Connection of ivermectin in cattle plasma and cattle dung and impact on non-target dung fauna. **a**, Simple linear regression ($Y = 16.585X$) through the origin ($R^2 = 0.83$), with 95% CI bands demonstrating the correlation between ivermectin concentrations in cattle dung (ng g⁻¹ dw) versus cattle plasma (ng ml⁻¹) for the long-acting IVM-BEPO formulation (data from 2–211 days after injection where both plasma and dung data are available). Dashed anchor lines indicate predicted concentrations in dung for previously determined 10-day LC₅₀ and LC₉₀ for *A. coluzzii*. **b**, Half-violin plots of aggregated EC₅₀ data from ecotoxicological single-species testing with dung beetles (mortality and

reproduction) and dung flies (mortality); n = number of findings from reviewed literature. The EC₅₀ dataset is detailed in Supplementary Table 6 and refers to the dry weight concentration in dung. Dotted lines and the shaded area are extended from the LC₅₀ and LC₉₀ values in **a** and illustrate a corridor of potential ivermectin release through dung of treated cattle. Whiskers in the kernel density plot show the standard deviation around the median (black line). All dung concentration measurements and EC₅₀ are reported on a dry weight basis to facilitate accurate comparisons across studies.

t -test comparison between formulations: $t = -1.17$, $P = 0.23$). Unlike IVOMECD, the depot formulation reached this level over 211 days (Fig. 2c, Supplementary Table 5 and Supplementary Fig. 2). The 10-day LC₉₀ differed significantly, with lower concentrations needed to cause 90% mortality with the depot (IVOMECD LC₉₀: 31.8 ± 2.8 ng ml⁻¹; IVM-BEPO LC₉₀: 19.2 ± 0.6 ng ml⁻¹; $t = 4.20$, $P < 0.001$).

Our vector population simulation model demonstrates that using ivermectin-treated cattle, combined with bed nets, reduces mosquito populations by 25 to over 90% (Fig. 3b,c; refined modelling scenarios in Supplementary Fig. M1). Model outputs predict increased effectiveness for both formulations when cattle outnumber humans as the host population and when vectors prefer animals. Treatments primarily affect infectious mosquitoes aged 10 days old or older since feeding likelihood on treated cattle and dying increases with age. The long-acting depot consistently reduces epidemiologically relevant vectors by over 50% for at least 6 months and peaks at 95% reduction. Multiple injections with IVOMECD are less effective, with vector populations cyclically increasing after peaks of 5–72% reduction.

Mosquito toxicity and ecotoxicological effects

Figure 4a shows ivermectin correlation in cattle plasma and dung after one injection of the depot formulation. Calculated 10-day LC₅₀ and LC₉₀ for *A. coluzzii* translate to predicted ivermectin concentrations in cattle dung ranging from 138–319 ng g⁻¹ dw. The mean $\pm$ s.d. excreted concentration, however, was higher at 337 ± 185 ng g⁻¹ dw ($n = 86$), corresponding to a mean plasma concentration of 19.1 ± 9.2 ng ml⁻¹, regardless of time. These concentrations were descriptively compared to ecotoxicological half maximal effective concentration (EC₅₀) data from standard tests (for example, refs. 30,31) with non-target dung beetles and flies (Fig. 4b and Supplementary Table 6). For a comparable formulation with similar release pattern under large-scale field conditions, predicted ivermectin concentrations in dung could exceed EC₅₀ values for most tested dung flies. For flies and beetles, only EC₅₀ data were compared, meaning that statistically, even lower concentrations could endanger a proportion of coprophagic arthropod communities³².

Effectively, Fig. 4b serves as preliminary risk estimation for dung fauna based on laboratory data.

Environmental fate of ivermectin

Figure 5a presents the particle size distribution and organic carbon (C_{org}) content of 30 agricultural soils from three Burkina Faso villages. Since sorption studies³³ were performed with fine soil (<2 mm), boxplots display the proportion of fine soil, considering high coarse-soil contents in many samples. Individual fine-soil analysis³⁴ revealed mostly loams, sandy loams and silt loams in the study region. The K_d sorption coefficients for six selected soils ranged from 55–123 ml g⁻¹, averaging 84.5 ml g⁻¹. Normalized to soil C_{org} , the K_{oc} sorption coefficients varied from 6,630–10,870 ml g⁻¹ (Supplementary Table 7). Sorption correlated significantly ($P < 0.05$) with C_{org} and pH value ($r = 0.86$ each) (Fig. 5b). Regarding dung storage for studying ivermectin dissipation (Fig. 5c), results were categorized into external and internal storage. Significant differences ($P < 0.01$) in ivermectin concentrations were observed in samples stored under internal laboratory conditions. Figure 5d displays mean ivermectin dissipation in internally stored samples. First-order kinetics describe the dissipation in stored dung. Including the day 0 concentration (normalized to unity), the fit through days 0, 30, 60 and 90 resulted in a degradation constant $k_1 = 0.00145$ (adj. $R^2 = 0.059$), 50% dissipation time (DT₅₀) = 478 and DT₉₀ = 1,588 days. With only days 30, 60 and 90, this fit yielded $k_1 = 0.00381$ (adj. $R^2 = 0.968$), DT₅₀ = 182 and DT₉₀ = 604 days in dung.

Discussion

Initially, we posed three questions (Fig. 1a) to also guide future ETL endeavours: (1) How can ivermectin-treated cattle complement malaria vector control? (2) What improvement on malaria vector control can be achieved with ivermectin-treated cattle? (3) How can we avoid ecological drawbacks in vulnerable agroecosystems?

Efficacy of a single-depot injection versus repeated injections

Considering our proof-of-concept²⁶, we adjusted the ivermectin formulation and statistical design. The long-acting formulation sustains

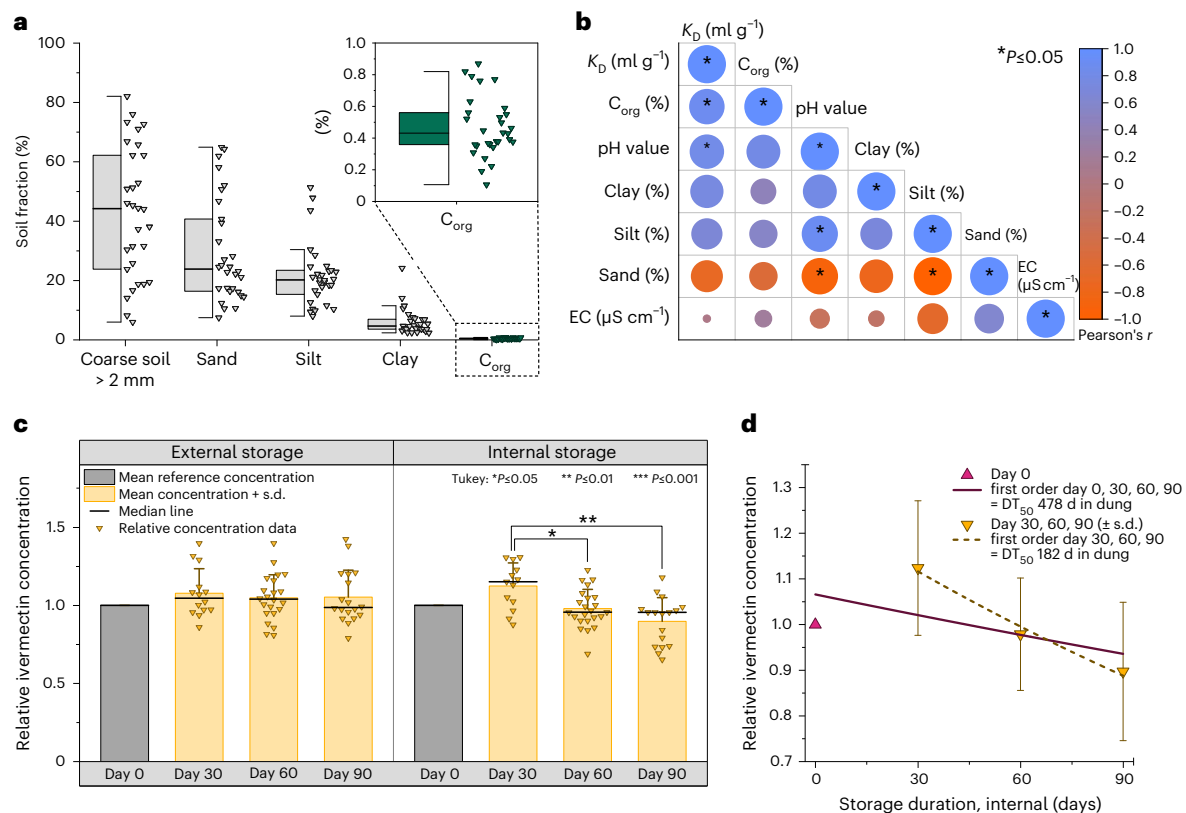


Fig. 5 | Soil properties, sorption correlation and degradation of ivermectin in stored dung samples. **a**, Particle size distribution and organic carbon (C_{org}) in topsoils ($n = 30$). Sand, silt, clay and C_{org} percentages are normalized to 100% to complement the coarse-soil fraction. Shown fine-soil distributions do not describe soil texture. The black line in boxes is the median, with boxes stretching from the 25th to the 75th percentile. Whiskers display the upper and lower inner fences. See Supplementary Table 12 for village-specific details. **b**, Correlation (Pearson's r) between linear K_d sorption coefficients and soil properties ($n = 6$ selected soils). Circle sizes represent absolute values of the correlation coefficient; $*P \leq 0.05$. EC, electrical conductivity. **c**, Relative ivermectin IVM-BEPO concentrations in stored dung ($n = 13$ – 23) related to storage time under external

(semi-field) and internal (insectary) conditions. Concentrations in stored dung are from timepoints DAI 2, 7, 75, 174 and 204 to cover the study duration. Respective day 0 concentrations are normalized to unity for comparison (two-sided Tukey pairwise mean comparison, with specific comparisons revealing: 30 days versus 60 days ($P = 0.02$), and 30 days versus 90 days ($P = 0.0002$); storage concentrations followed a normal distribution ($P < 0.05$)). **d**, Modelled dissipation in stored dung (internal conditions) following simple first-order kinetics, with x axis from -3 to 93 and y axis abridged. DT_{50} and DT_{90} show the predicted time (days) for 50% and 90%, respectively, of the initial ivermectin concentration to dissipate. Day 0 concentration normalized to unity. Days 30, 60 and 90 show mean $\pm$ s.d. of $n = 13$, 23 and 17 stored dung samples, respectively.

ivermectin release over at least 6 months. Although the release pattern and dose need adjustment to refine the release period, the potential long-term efficacy meets WHO criteria for malaria transmission control with endectocides³⁵. The slow release of ivermectin from the subcutaneous depot leads to a rate of absorption in blood lower than the rate of elimination from the body. The lipophilicity of ivermectin causes high volumes of distribution in animals and accumulation in target tissues, acting as secondary drug reservoir²¹. Hence, concentrations of ivermectin and metabolites in subcutaneous fat tissue may remain high in IVM-BEPO-treated cattle, enhancing effectiveness.

The zoophagic proportion in mosquito populations, relevant for residual *Plasmodium* transmission¹¹, can increase with widespread LLIN use³⁶. In southwestern Burkina Faso, populations of the major vector *A. coluzzii* show opportunistic blood-feeding behaviour, with over 50% feeding on alternative animal hosts, while their innate feeding preference remains toward humans³⁶. Our approach with ivermectin-treated cattle addresses these zoophagic vector compartments of malaria transmission, which are not yet considered in conventional anthropocentric malaria control programmes³⁵. The long-acting ivermectin formulation mitigates logistical and cost challenges of repeated injections, offering a stronger barrier against malaria transmission by preventing vector population resurgence between treatments. While zooprophylaxis against malaria is a complex concept, leaning towards zoopotentialization depending on transmission context³⁷, our

approach capitalizes on existing cattle, rendering their blood toxic to opportunistic and zoophagic mosquitoes while improving cattle health and milk production²⁰.

ETL impact on vector populations could be greater than modelled since ivermectin is also toxic to traits influencing fitness other than survival³⁸. Moreover, opportunistic vectors failing to feed on net-protected humans and seeking alternative hosts are not addressed in our model. Overall, effectiveness depends on the human blood index (HBI), indicating the proportion of mosquito populations feeding on humans. Blood feeding tendencies should therefore be characterized before ETL field deployment, especially since livestock other than cattle could represent alternative hosts. Effectiveness also relies on local livestock density and the treated herd fraction.

Moreover, ETL evaluation should consider veterinary benefits through parasite control and incorporate realistic animal populations into models, including gestating and lactating females, and animals for consumption (meat and milk³⁹). Following Joint FAO/WHO Expert Committee on Food Additives⁴⁰ guidelines and involving animal owners is essential.

Ecotoxicological considerations

Ivermectin's capacity to control vectors holds promise for mitigating malaria and improving animal health and productivity^{15,18}. However, vigilance is required concerning potential environmental consequences.

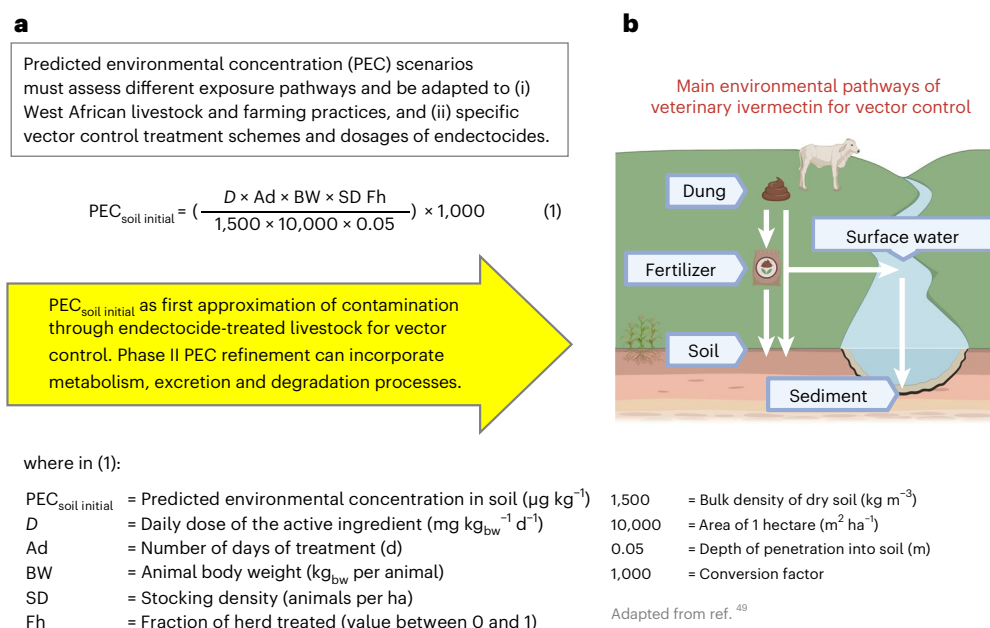


Fig. 6 | Exposure assessment as the initial step of environmental risk assessment for endectocide-based approaches to control opportunistic and zoophagic malaria vectors. **a**, Equation (1) for $PEC_{\text{soil initial}}$ is based on ref. ⁴⁹. Exemplary parameters for a 211-day pasture scenario: $D = 0.0019$, $Ad = 211$, $BW = 160$, $SD = 9.5$, $Fh = 1$. Phase I screens products and includes initial PEC estimations, while Phase II conducts detailed assessments using refined data, field studies and modelling. Fh , the treated herd fraction, is notably relevant for refugia⁵¹ incorporation to manage resistance in vectors and parasites.

b, Exposure assessment of endectocides used for vector control, such as ivermectin, must consider various pathways, including direct excretion or dung use as fertilizer for potential drug residue transfer into agricultural soils. Soil contamination is also conceivable on adjacent unmanaged soils. Contamination of surface water and sediment can occur through run-off, erosion or direct excretion, potentially exposing aquatic fauna and larval vectors to ivermectin. Figure 6b was created with [BioRender.com](https://www.biorender.com).

Comprehensive research spanning over 30 years has consistently flagged non-target effects of ivermectin and other avermectins on dung and soil biota^{22–25,41}.

In a preliminary assessment via literature review, plasma concentrations lethal to 50–90% of mosquitoes (Fig. 4) could produce excreted ivermectin levels harmful to most dung insects. However, it is important to recognize limitations of laboratory data and seek validation in field scenarios. Notably, a landscape-field study²⁵ confirmed ivermectin effects on non-target fauna and emphasized the importance of spatio-temporal realism in environmental assessments. For the related endectocide eprinomectin, cattle treated with a long-acting injectable formulation excreted residues for over 25 weeks, suppressing dung-breeding insects and reducing insect diversity²⁸. While much current literature centres on temperate and Mediterranean species, a clear knowledge gap persists concerning West Africa, and few studies assess impacts on (sub-)tropical entomofauna, indicating an urgent research objective.

The use of veterinary ivermectin reportedly carries adverse implications for dung fauna biodiversity and ecosystem functioning^{42–44}. Given these potential ecotoxicological impacts, the precautionary principle becomes a guiding factor to proactively address and mitigate risks to biodiversity and ecosystem health in West African agroecosystems. This is especially imperative considering the scarcity of research on the ecological impacts of long-acting injectable ivermectin formulations.

Environmental fate of ivermectin and exposure assessment

Our K_D and K_{OC} soil sorption coefficients, the first for Burkina Faso, align with previous reports^{22,45}. Strong, mostly irreversible ivermectin sorption⁴⁵, emphasizes reduced mobility and availability. However, sorption tests are conducted with fine soil³³, potentially overestimating sorption in tropical soils with abundant coarse soil and limited surface area.

Ivermectin is moderately persistent, and dissipation in soil and manure increases under warm, aerobic and humid conditions^{46,47}. In soils, comparable models projected DT_{50} of 16–67 days at 20 °C and

89–105 days at 6 °C (ref. ⁴⁷) and from 10–16 days⁴⁸. In soil–manure mixtures, DT_{50} ranges from 7–240 days⁴⁷. These authors concluded that sorption influences dissipation and even under aerobic conditions, ivermectin dissipation in soils is relatively slow⁴⁷. Our dissipation results in cattle dung indicate persistence under these conditions. Storage during dry seasons may lead to reduced dissipation and could preserve ivermectin until the next cultivation period when dung is utilized as fertilizer. Increasing ivermectin concentrations in dung after 30 days (Fig. 5c) presumably show relative enrichments because readily degradable organic matter decomposes while ivermectin remains. In soils, ivermectin dissipation fluctuates with climatic conditions^{46–48}, and its behaviour under sub-Saharan climates remains ambiguous. In West African soils, weaker sorption and higher temperatures might accelerate dissipation. However, data on ivermectin's environmental fate under ETL scenarios, especially within soil–dung mixtures during seasonal rainfall, are lacking. Consequently, managing ivermectin residues should also account for climatic conditions, encompassing Sahelian, Sudanian and Guinean zones.

In the European Union, environmental risk assessment during veterinary pharmaceutical registration involves estimating a predicted environmental concentration (PEC)^{32,49}. This process utilizes a toolbox spanning Phase I and Phase II assessments. An initial step in ecotoxicological oversight of ETL should establish PECs in dung, soils, dung–soil mixtures, surface waters and sediments (Fig. 6). Here, dung fauna exposure was estimated using measured ivermectin concentrations in dung (Fig. 4b).

To transfer exposure from dung to soil, an exemplary $PEC_{\text{soil initial}}$ was calculated at $4.86 \mu\text{g kg}^{-1}$ for the long-acting formulation dosed at 2.4 mg kg^{-1} . This compares to reported PECs for pasture grazing²². However, estimating and refining soil PECs varies with livestock treatment and data availability^{22,49}, making assessments challenging without defined treatment scenarios. The longer release of long-acting formulations is especially critical. Since dung is a valuable agricultural

resource in many malaria endemic zones where breeding and agricultural practices are integrated, responsible dung management remains imperative.

Environmental risk mitigation

Ecotoxicological guidance for ivermectin-based vector control should encompass exposure assessment, effect assessment, risk assessment and risk mitigation measures (RMMs). Integrating these tools with vector control measures can yield synergies and improve cost effectiveness. Should ivermectin contaminate puddles or surface waters, minor degradation is anticipated, but more likely rapid dissipation and sorption into the sediment^{22,45}. Ivermectin degradation through photolysis²² in dung patties or soils is limited to upper layers. In our external storage experiment, samples were shielded from sunlight (Extended Data Fig. 1c). However, given common agricultural practices of incorporating dung into soils, substantial sunlight exposure for excreted drugs is unlikely.

For veterinary pharmaceuticals, RMMs to reduce environmental risks for non-target fauna are already conceptualized^{32,50}. Importantly, RMMs synergize with measures to reduce resistance in livestock parasites and facilitate sustainable parasite control. Reducing ivermectin distribution with RMMs also limits contact for adult and larval vectors, mitigating resistance selection pressure. Modifying previous recommendations⁵⁰, RMMs for ETL should respect local conditions and could be guided by these principles:

- (1) Prevent drug entry into surface waters.
- (2) Corral treated animals whenever possible.
- (3) Leave fractions of the herd periodically untreated to create refugia⁵¹. This allows safe consumption (meat and milk) and reduces resistance pressure and non-target fauna risks.
- (4) Implement measures of animal performance and routine diagnostics for early detection of ivermectin-resistant parasites, aligning livestock health and vector control goals while minimizing drug use and environmental exposure.
- (5) Capitalize on existing agro-pastoral systems of dung collection and store dung under conditions that promote drug degradation.
- (6) Avoid repeated application of dung with drug residues as fertilizer if long-term effects on non-target fauna are unknown.

In our study region of Burkina Faso, manure storage pits called ‘fosses fumières’ are common (Extended Data Fig. 1a). Pits are excavated near settlements and filled with dung, crop residues and kitchen waste during dry seasons. They are later emptied and the mixture is spread as fertilizer in the following cultivation period. We encourage exploring composting conditions in these pits for potential ivermectin degradation. However, ivermectin residues and their associated toxicity may not completely dissipate during storage⁵². Adapting RMMs designed for temperate climates and pasture scenarios while respecting agricultural practices in West Africa remains fundamental. This also requires training opportunities for herders and veterinarians.

Side effects on plants

Regarding potential effects of ivermectin on crops, limited research exploring phytotoxicity is available for real-world environments. Some reports^{24,33} considered that via livestock, ivermectin may affect plants. Since this concern is mostly undiscussed for West Africa, caution is appropriate. For Burkina Faso, potential effects on local varieties of corn, sorghum, cotton or millet (Extended Data Fig. 2b) should be investigated under field scenarios with tropical soils.

Potential ivermectin-induced mosquito resistance

Human and animal intakes can alter volatile plume signatures, influencing *Anopheles* vector host recognition⁵⁴. With ETL, changed animal odour may affect host attractiveness or repellency, raising ethical

concerns about redirecting opportunistic mosquitoes toward humans. Although ETL targets adult female mosquitoes, resistance to lethal ivermectin concentrations in populations may develop through selection pressures. These arise from adult females ingesting ivermectin during blood feeding and larvae exposure to ivermectin-contaminated dung in surface waters. Large-scale ETL deployments should also incorporate phenotypic diagnostic tools for on-field mosquito resistance monitoring⁵⁵.

Notably, our approach inherently incorporates refugia: not treating entire herds creates a refuge for susceptible parasites, aligning with known strategies for mitigating anthelmintic resistance⁵¹. This fortifies the efficacy and sustainability of ETL solutions.

Towards sustainability in vector control

The One Health Joint Plan of Action (2022–2026) by FAO, UNEP, WHO and WOA consolidates that ‘health of the environment is a critical foundation for the health and well-being of humans, animals and plants’⁴. Aligned with a modern, non-anthropocentric view of human health, this emphasizes the need for ecological equity⁵⁶. Therefore, vector control approaches based on endectocides must equally consider socio-economic realities, as well as human, animal and environmental health dimensions.

Ecotoxicological guidance addresses environmental impacts of ETL and underscores the importance of biodiversity, soil health and sustainable resource management. Integrating traditional organic waste management (for example, fosses fumières) with scientific advancements could optimize composting and drug degradation. This engages communities and strengthens nutrient cycles and soil resilience against erosion and climate change. Protecting non-target fauna and enhancing soil carbon balances can mitigate risks to biodiversity and ecosystem services. Echoing Rachel Carson’s sentiments in ‘Silent Spring’ on health risks of insecticides, ‘...prevention is the imperative need’¹ is a notion equally applicable to environmental health.

We demonstrate that long-acting ivermectin formulations for cattle can transform malaria vector control. This strategy meets WHO efficacy criteria, remarkably improves animal health and potentially extends control over other arthropod-borne zoonotic diseases.

Our unique multidisciplinary approach, embedding comprehensive modelling, an innovative formulation and ecotoxicological insights promises a new aspect of sustainable vector control. Before widespread implementation, potential ecotoxicological risks associated with ivermectin residues in dung demand careful consideration. We recommend: (1) studying ivermectin degradation in manure pits; (2) characterizing the entomofauna of West African agroecosystems; and (3) initiating ecotoxicological routines in West Africa to identify potential ecological consequences.

In addition, we propose actionable, bottom-up and region-specific risk mitigation strategies. If endectocide-treated cattle become routine in vector control, interdisciplinary research, generational knowledge and ecotoxicological insights must converge to create locally adapted, environmentally mindful solutions. Bridging the research–policy gap is essential to establishing necessary regulatory frameworks to translate research into sustainable action.

Methods

Layout of the study design

We randomly assigned 24 male cattle into three study arms: 8 were treated with monthly injections of a commercial IVOMEC-D ivermectin formulation, 8 received the long-acting IVM-BEPO ivermectin formulation and 8 had no ivermectin treatment (control). An animal from each arm was put aside as spare animal (data from 7 cattle per arm were then further collected). Doses were based on cattle body weight (bw) on injection day: 0.4 mg kg^{−1} bw for monthly IVOMEC-D injections and 2.4 mg kg^{−1} bw for a single IVM-BEPO injection at study start. These

doses were doubled on the basis of our previous data^{26,27} to increase efficacy and remanence. Injections were administered by veterinary technicians. Study duration was 34 weeks (Fig. 1). We sampled cattle blood plasma and dung to determine ivermectin pharmacokinetics and performed skin-feeding assays on cattle to assess mosquito mortality as a proxy for formulation efficacy. Selected dung samples were stored to determine ivermectin degradation. Soils from southwestern Burkina Faso were sampled to assess ivermectin sorption.

Ivermectin formulations, dosage and injections

The long-acting injectable formulation was built on BEPO technology⁵⁷, an injectable in situ-forming depot technology based on biodegradable copolymers. Following subcutaneous injection, the block copolymers precipitate upon contact with body fluids, thereby entrapping the therapeutic molecule within the formed polymeric solid matrix (the depot). The depot progressively bioresorbs while delivering the active pharmaceutical ingredient with the desired pharmacokinetics. The same technology has been used to assess the macro- and microfilaricidal efficacy of a 12-month ivermectin formulation prototype against *Onchocerca ochengi*⁵⁸ and as a proof-of-concept, tested against *A. coluzzii*²⁷.

The IVM-BEPO formulation was selected from a preliminary study²⁷ and composed of 45% (w/w) copolymer comprising a tri-block PLA₉₇-PEG₄₅-PLA₉₇ and a di-block mPEG₄₅-PLA₁₃₀, 5% (w/w) ivermectin and 50% (w/w) dimethyl sulfoxide (DMSO). The formulation was designed to release ivermectin for at least 6 months. Before preparation, the tri- and di-block copolymers of the formulation were preliminarily dissolved overnight in DMSO (Procipient, Gaylord Chemical) at room temperature and under continuous stirring. Then, ivermectin (Fagron) was added to the polymer solution until complete dissolution. The formulation was sterile filtered using 0.2 µm filters (Minisart SRP 15, Sartorius) and then administered to cattle according to their bw (2.4 mg of ivermectin kg⁻¹ bw, that is, 48 mg of formulation kg⁻¹ bw) with a hypodermic syringe capped with a 16-gauge needle. Volumes were adjusted to the weight each cattle was expected to reach 3 months after the injection (mid experimental time) to consider potential dilution of the product due to animal growth. Expected weight gains were calculated from weighing performed before treatments in January and April 2019 (Supplementary Table 8). A 25% increase in 3 months was estimated for cattle below 130 kg, 15% for cattle weighing 130–170 kg and 10% for the heaviest cattle (>170 kg). Weights and corresponding volumes of the long-acting formulation injected per cattle and per treatment were calculated accordingly (Supplementary Table 9). The long-acting formulation was imported into Burkina Faso under clearance provided by the 'Direction Générale des Services Vétérinaires' of Burkina Faso (Visa from the 'Direction de la Santé Publique Vétérinaire et de la Législation' issued 11 January 2019).

The IVOMEC-D injectable veterinary formulation was used at a dose of 0.4 mg kg⁻¹ bw and injected each month subcutaneously (Fig. 1b) using a hypodermic syringe capped with an 18-gauge needle. Cattle were weighed before each treatment to adjust injection volumes (Supplementary Table 10). Remaining cattle from the experiment were weighed each month as well. Weight gain of all cattle was examined to ensure their well-being and to identify potential treatment effects (generalized linear modelling; Supplementary Fig. 3). For both formulations, the ivermectin dose was selected on the basis of experiences from our previous studies^{26,27}.

Ethics oversight

The study received approval from the CIRDES ethics committee under letter no. 15/CE-CIRDES/16-10-2018.

Cattle care, blood and dung sampling

All cattle were crossbred Soudanese Fulani Zebu × Baoulé Taurine and were kept at the Centre International de Recherche-Développement sur l'Élevage en zone Subhumide (CIRDES) in Bobo-Dioulasso, Burkina

Faso. One month before the experiment started, animals were moved into a net-protected stable and received a veterinary examination and prophylactic treatment with diminazene aceturate (Berenil2000, 3.5 mg kg⁻¹ bw) against trypanosomiasis and albendazole (one bolus Benzal 2,500 mg per animal) against gastrointestinal parasites. The latter was chosen over ivermectin to avoid cross-contamination in later sampling. At the beginning of the study, mean cattle age was 3 years and mean weight was 122 kg (cattle were weighed monthly). Stable openings were closed by fine-meshed filtering tissue to protect cattle from insects and outside animals. Cattle were checked daily by cowherds for signs of parasite infestation or disease symptoms and before each mosquito blood-feeding experiment by veterinary engineers (engineers checked for clinical signs of apthae, cough, nasal discharge, slime, anaemia, recumbent position, anorexia, diarrhoea, fever, scabies). There was no incidence of any symptoms during the whole experiment. Unfortunately, an animal from the IVM-BEPO group died following an accident with a stable box barrier that fell on its head at night. This happened 3 months after treatment. The animal was replaced by the spared animal from the same treatment.

According to local recommendations⁵⁹, cattle were fed twice daily with rice straw and cotton cake (5 kg and 1 kg in total per animal, respectively). Water and a mineral complement block were offered ad libitum. Blood samples were collected from the jugular vein with 5 ml heparin tubes at the timepoints given in Fig. 1b. Plasma was immediately collected after sample centrifugation at 1,500 g for 15 min, and stored at -20 °C until further processing. Dung samples were collected directly from the cattle rectum or on freshly deposited dung synchronously with plasma. We constituted samples (30 g each) for ivermectin dosage on fresh dung and on dung after storage. For IVM-BEPO dung samples, fresh dung was distributed in plastic vials in two groups and according to the intended storage duration (30, 60 or 90 days). One group was inside the insectary (to mimic steady, fresh and humid conditions) and the other outdoors (exposed to dry season conditions). Plastic vials were covered with a piece of bed net (Extended Data Fig. 1c). Environmental conditions in the insectary were measured daily and were 26 ± 2 °C and 75 ± 5% relative humidity. For external storage, daily and nightly temperatures during the respective storage periods are given in Supplementary Table 11 (from ref. 60). Mean outdoor temperatures ranged from 32.1–39.6 °C during the day and from 17.9–22.8 °C at night. After fresh sampling or storage, dung samples were kept at -20 °C for a minimum of 24 h, freeze dried for 24 h, ground for 15 min using a mortar and pestle, disposed into labelled plastic bags and stored at -20 °C before chemical analysis.

Mosquito protocol

An *A. coluzzii* mosquito colony was established between February and March 2019 in the insectary of CIRDES in collaboration with the Institut de Recherche en Sciences de la Santé. Wild blood-fed females were collected in dwellings of the Kou Valley, 50 km northwest of Bobo-Dioulasso in southwestern Burkina Faso. Mosquito breeding and direct skin-feeding assays on cattle (Extended Data Fig. 2a,b) followed a previously reported procedure²⁶, except that mosquitoes received a 10% glucose feeding solution instead of 5%. Exposure took place in 20 instances, including one pre-treatment to test for potential cattle confounding effects on mosquito survival (Fig. 1b). All 24 cattle were included in this pre-treatment study. Overall survival was assessed in 15,637 fully engorged females that were followed from days 1–30 post feeding. The targeted number of females per cattle and time point was 40, distributed in lots of 10 in 4 white cardboard cages (V = 200 cm³) covered with an untreated mosquito net fixed using a rubber band. Each day, the number of dead females was counted and surviving females at the end of the experiment were also counted. Mosquito survival analysis data, sample sizes and the R code are available on GitHub at <https://github.com/angeliqueporciani/ANIVERMATE>.

Soil sampling and characterization

Soil samples were taken in Tuy Province, southwestern Burkina Faso, in the villages of Sébédougou, Waly and Kari (Extended Data Fig. 2a). We aimed to sample a representative variety of Burkinabé arable soils under comparable climatic conditions. At each village, we sampled ten fields currently used for regional crops. On each field, five disturbed soil samples were taken with an auger at 0–15 cm depth and mixed for a composite sample. Soil properties were derived from field notes and harmonized into WRB soil classification⁶¹. Laboratory analyses were performed for soil pH value (0.01 M CaCl₂), electrical conductivity, coarse-soil fraction, particle size distribution and C:N ratio. Carbonate content was estimated following the semi-quantitative preparation step of EN ISO 10693:2014, which indicated no inorganic carbon present. Thus, C_{total} from C:N measurements with a UNICUBE trace CN elemental analyser was used as a substitute for organic carbon (C_{org}). A complete characterization of sampled locations and soils is given in Supplementary Tables 12 and 13. Furthermore, six soil profiles were described in the sampled locations and brief descriptions are provided in Supplementary Figs. 4–9. Soil samples were transported under clearance provided by the RP Gießen, Pflanzenschutzdienst, Germany (issued 26 September 2019) and the Direction de la protection des végétaux et du contrôle des végétaux alimentaires et des Pesticides, Burkina Faso (issued 5 November 2019).

Environmental studies

To address the environmental fate of ivermectin after excretion, we conducted soil sorption studies and monitored ivermectin degradation in stored dung samples over 90 days. Sorption experiments and derivation of linear distribution coefficients K_D and K_{OC} were based on ref. 33 and published methods^{45,46}. Correlation (Pearson's r) between linear K_D sorption coefficients and soil properties was described with the OriginPro 2022 application Correlation Plot (v.1.31). Storage of dung samples was conducted in Burkina Faso under external, semi-field conditions and internal, laboratory storage (see above). These samples were eventually analysed for ivermectin after 30, 60 and 90 days of storage, and concentrations were compared (two-sided Tukey pairwise mean comparison, in OriginPro, v.2022 (64 bit)) to each other and their respective day-zero concentration. Concentrations in stored dung were normally distributed (Shapiro–Wilk, $\alpha = 0.05$, all $P > 0.05$). Next, we applied simple first-order kinetics to approximate future ivermectin concentration changes in stored dung, using the results from the internal storage experiment. Underlying methods are elaborated upon in ref. 47. The resulting degradation constant, or rate constant, k_1 , was used to estimate ivermectin dissipation over time. The time to reach 50% of the initial concentration is expressed as $DT_{50} = \ln 2/k_1$, while the corresponding DT_{90} equals $\ln 10/k_1$ (ref. 47). OriginPro v.2022 (64 bit) was used to create Figs. 2a–c, 3a, 4a–b and 5a–d.

Chemical ivermectin analysis

Extraction and quantification of ivermectin were based on existing techniques^{46,62} and harmonized for plasma and dung samples in this study. For quantitative determination, we used high-performance liquid chromatography (HPLC) with fluorescence detection after derivatization. The complete protocols are listed in Supplementary Table 15 and the accompanying supplemental text. In essence, samples (thawed plasma, freeze-dried dung) were fortified with an internal surrogate standard (doramectin) and extracted with acetonitrile. After ultrasound-assisted extraction and then centrifugation at 3,865 g, an aliquot of each supernatant was evaporated, reconstituted in acetonitrile and filtered. For HPLC fluorescence detection, ivermectin was derivatized with *N*-methylimidazole/acetonitrile (1:1 v/v), triethylamine, trifluoroacetic anhydride/acetonitrile (1:1 v/v) and trifluoroacetic acid according to reported procedure⁴⁶. Samples were quantified on an Agilent 1200 HPLC system with gradient elution (acetonitrile and purified water) on a reverse-phase, C18 column. Fluorescence detector

wavelengths were 364 nm for excitation and 463 nm for emission. Extraction recoveries (mean $\pm$ s.d.) of the surrogate doramectin were $106.5 \pm 21\%$ in plasma and $103.2 \pm 19.7\%$ in dung samples. Each plasma or dung sample was divided into two technical replicates that were extracted and measured individually. Analytical limits of detection (LOD) and quantification (LOQ) were calculated as described in ref. 45: $LOD = 1.47 \text{ ng ml}^{-1}$ in plasma, 5.05 ng g^{-1} dw in dung; $LOQ = 4.47 \text{ ng ml}^{-1}$ in plasma and 15.31 ng g^{-1} dw in dung. Measured concentrations $< LOQ$ were replaced with half the LOQ for further calculations. Data analysis was performed with ChemStation for LC 3D systems Rev. B.04.01 [481] and Microsoft Excel for Office 365.

Statistical analysis, mosquito survival and modelling

All statistical analyses and modelling were performed using R v.4.0.1 (18 May 2021, platform x86_64-apple-darwin17.0 (64 bit), ref. 63). The data and the R code are available in the referred repository, and the general methodology is described in the Supplementary Information Modelling chapter.

Pharmacokinetic parameters for plasma and dung concentration (maximum concentration (C_{max} ; peak plasma level), time to reach maximum concentration (T_{max}), apparent elimination half-life (half-life; time for plasma concentration to be reduced by 50%), and area under the curve (AUC; total drug exposure over time)) were estimated with noncompartmental analysis using the package PKNCA (v.0.9.5, ref. 64). For the commercial formulation, parameters were estimated using data from the first 28 days, whereas for the long-acting formulation, data until 211 days after injection were used.

Our study was designed to detect hazard ratios from 1.5 and upwards, with a power of 0.9 and a type I error rate of 0.05. The sample size needed to detect this size effect was 171 individuals, which we obtained by exposing at least 40 mosquitoes on each of the 7 cattle of each arm (at least 280 mosquitoes per arm). In comparison, a sample size of 16 mosquitoes is needed to detect a hazard ratio of 4, which meets WHO criteria³⁵ (hazard ratio ≥ 4) of endectocide products for malaria transmission control.

Kaplan–Meier survival curves and a Cox proportional hazards mixed model with cattle as a random effect were used to investigate mosquito survival differences between cattle clustered by experimental arm. Median survival times with 95% confidence intervals (CI) were plotted. Hazard ratios with associated P values were estimated before treatment and at each time point where mosquitoes were exposed for direct skin-feeding assays during the treatment efficacy follow-up (Supplementary Table 4).

We further explored the efficacy of the two formulations by considering the probability that a mosquito ingesting a blood meal containing ivermectin dies before becoming infected with *P. falciparum* sporozoites. The dose effect of ivermectin concentration on mosquito survival probability until a given day post ingestion of blood from treated animals (7, 10 or 13 days) was assessed using a multivariate log-logistic regression model with four input parameters. The lethal ivermectin concentrations inducing 7, 10 and 13-day cumulative LC₅₀ and LC₉₀ mosquito mortalities were estimated for each scenario and each treatment (Supplementary Table 5).

A modelling approach was developed to predict, in the field, the efficiency of ivermectin formulations in decreasing vector populations that transmit *P. falciparum*, with emphasis on ivermectin efficiency against infectious vectors. Efficiency was predicted under different field contexts relative to the proportion of cattle in a human–cattle host population, the long-lasting insecticide-impregnated net usage by human hosts (LLIN use proportion) and the intrinsic vector feeding preference (as measured experimentally using a dual-choice olfactometer). Four mathematical models were combined: (1) a generalized additive model and a one-compartment pharmacokinetic model describing the ivermectin cattle plasma concentration dynamics; (2) a Cox proportional hazards model to describe how this dynamic

impacts mosquito survival; (3) a deterministic mosquito *P. falciparum* transmission model (the susceptible-exposed-infectious malaria transmission model from ref. 65), modified to take into account 2 host species (cattle and human) and 2 vector control interventions (the use of LLINs to protect humans and the injection of ivermectin formulations into cattle hosts); and (4) a vector behaviour model to take into account the mosquito intrinsic feeding preference and the probability of dying when encountering an LLIN. These models were all fed using parameters from the present study and parameters taken from the literature. The model descriptions, equations and parameters with the corresponding values used to feed the models are given and detailed in the Supplementary Information Modelling chapter.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data and methods supporting the article are available in the Supplementary Information. All data are also available upon reasonable request. Relevant raw data for Figs. 2–5 are listed in Excel files and provided as source data files. References for EC₅₀ data from ecotoxicological standard tests (Fig. 4b) are provided in Supplementary Table 6. Outdoor temperature data were sourced online from NASA LP DAAC (MYD11A1 MODIS/Aqua Land Surface Temperature/Emissivity Daily L3 Global 1 km SIN Grid V006). Statistical analyses and modeling for Fig. 3 were performed using R v.4.0.1. Data (incl. mosquito survival analysis data and sample sizes) are available in the ANIVERMATE repository on GitHub at <https://github.com/angeliqueporciani/ANIVERMATE>, and additional methodology is described in the Supplementary Information. Source data are provided with this paper.

Code availability

The relevant R codes are available via GitHub at <https://github.com/angeliqueporciani/ANIVERMATE>.

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Author contributions

A.P.H., S.H.P., C.R., M.-S.M., A.-L.C., R.K.D., J.R., R.-A.D. and K.M. conceptualized the study and experiments. A.P.H., S.H.P., A.P., C.R., A.-L.C., N.M., R.K.D., R.-A.D. and K.M. developed the methodology. A.P.H., S.H.P., L.Z., A.S. and M.-S.M. were involved in the investigation. A.P.H., S.H.P., A.P., A.S. and N.M. conducted formal analysis. A.P. and N.M. managed the software. A.P.H., S.H.P., A.P. and L.Z. curated data. C.R., A.-L.C., R.K.D., R.-A.D. and K.M. provided resources. A.P.H., A.P. and K.M. performed visualization. A.P.H., S.H.P., A.P. and J.R. performed validation. R.K.D., R.-A.D. and K.M. administered the project. R.-A.D. and K.M. jointly supervised and conceived the project and acquired the funding. A.P.H. and K.M. wrote the original draft. All authors wrote, reviewed and edited the paper.

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Competing interests

The patent related to the long-acting depot formulation used in this study has the number WO2012/090070 and belongs to Medincell S.A., Jacou, France. C.R. is still an employee and shareholder of Medincell S.A. M.-S.M. and A.-L.C. are former employees and still shareholders of Medincell S.A. All authors and contributors currently or formerly employed at Medincell S.A. did not influence or contribute to sample collection, data collection, sample analysis, data analysis, evaluation, risk assessment, decision to publish, or conclusions presented in this paper. The other authors declare no competing interests.

Additional information

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Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41893-024-01332-8>.

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a



b



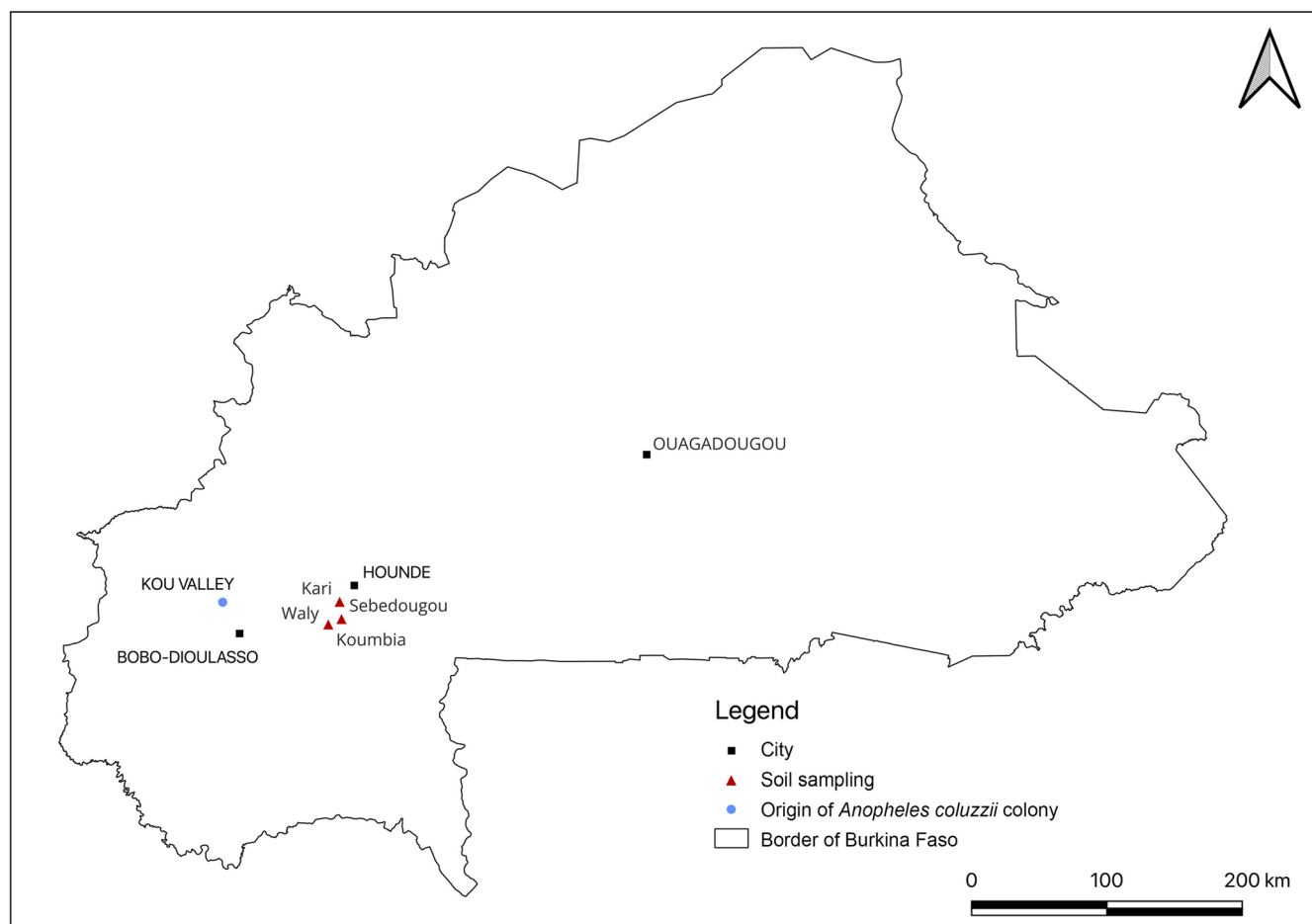
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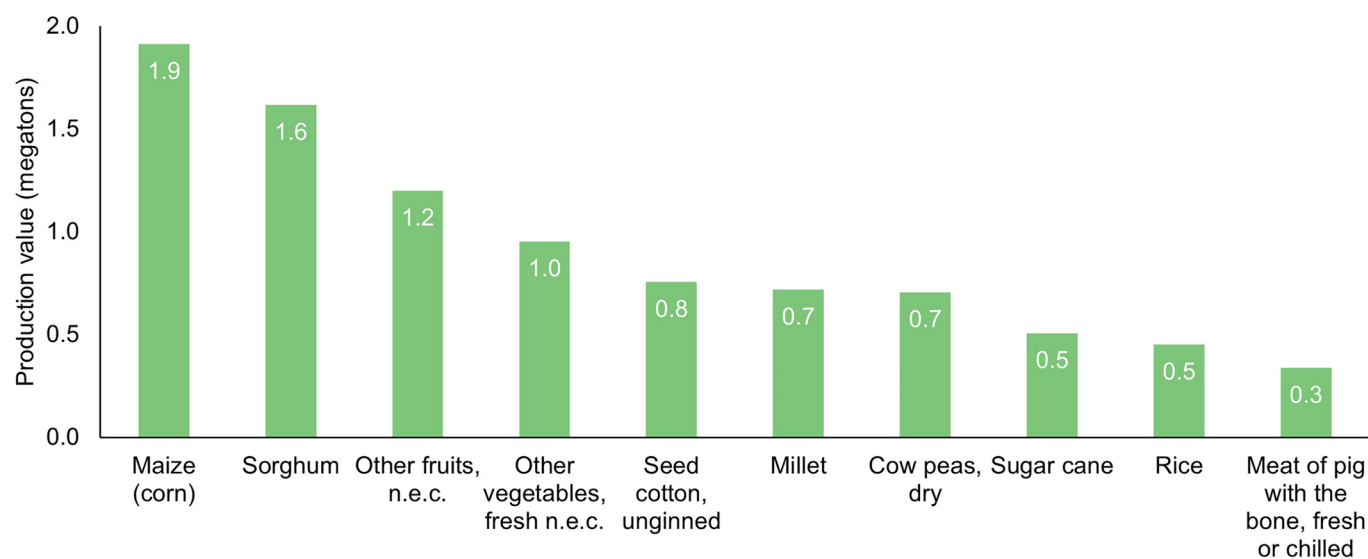
Extended Data Fig. 1 | Additional photography to illustrate manure pits for composting in Burkina Faso, mosquito skin-feeding assays, and external storage of dung samples. **a**, Photographed example of a fosse fumiére (a manure pit) in Burkina Faso containing cattle dung. The fosse fumiére is generally dug in the field near a homestead. The dimensions are approximately 3 m on each side and 1.2 m depth. It is filled mainly during the dry season with animal dung, crop residues, and other kitchen waste. The pit is emptied before the beginning

of the cultivation period to spread the dung-mixture on fields. **b**, Arrangement for keeping cattle during the mosquito blood meal (skin-feeding assay). The mosquitoes are contained in small plastic bowls attached to the animal flank. **c**, Outdoor storage of cattle dung samples. The dung was kept in plastic bottles covered with mosquito net fabric and placed in a shaded area outside the stable. **a–c**, Photo credit: Hermann Sié Pooda. Panel (b) shows Saïdou Boly, who gave formal consent for his image to be published.

a



b



Extended Data Fig. 2 | Geographic overview, map of Burkina Faso, and agricultural production. a, The Centre International de Recherche-Développement sur l'Élevage en zone Subhumide (CIRDES) and Institut de Recherche en Sciences de la Santé (IRSS) are located in Bobo-Dioulasso. Soil samples were taken east of Bobo-Dioulasso in three villages in the region

of Koumbia. The experimental mosquito colony was established from wild mosquitoes caught northwest of Bobo-Dioulasso in dwellings of the Kou Valley. b, Top commodities production in Burkina Faso in 2021, modified plot after FAO raw data (n.e.c. = not elsewhere classified).

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Software and code

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Data collection No software was used for data collection.

Data analysis R, version 4.0.1 (2021-05-18, platform x86_64-apple-darwin17.0 (64-bit)), including the package PKNCA (version 0.9.5); OriginPro, version 2022 (64-bit) SR1, including the application Correlation Plot (v1.31); ChemStation for LC 3D systems Rev. B.04.01 [481]; Microsoft Excel for Office 365. The R Code is available at <https://github.com/angeliqueporciani/ANIVERMATE>

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The data supporting the article are available in the Supplementary Information. All data are also available upon reasonable request. Relevant raw data for Figs. 2–5 are listed in Excel files and provided as source or supplementary data files. Source data are provided with this paper. Figures 1 and 6b were created with BioRender

(BioRender.com). References for EC50 data from ecotoxicological standard tests (figure 4b) are provided in Supplementary Table 6. Outdoor temperature data were sourced online from NASA LP DAAC (MYD11A1 MODIS/Aqua Land Surface Temperature/Emissivity Daily L3 Global 1km SIN Grid V006). Statistical analyses and modeling for figure 3 were performed using R, version 4.0.1.; Data (incl. mosquito survival analysis data and sample sizes) are available in the ANIVERMATE repository, and additional methodology is described in the Supplementary Information file. Link to the GitHub repository: <https://github.com/angeliqueporciani/ANIVERMATE>

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Ecological, evolutionary & environmental sciences study design

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Study description	This study was designed to measure the efficacy and environmental risks of a One Health vector control approach using ivermectin against malaria mosquitoes. The study had three experimental arms (control, commercial ivermectin formulation, novel long-acting ivermectin formulation) with seven cattle per arm. We also considered environmental side-effects of ivermectin treatment and risk assessment. Mosquito survival data were transferred into a malaria transmission model to predict efficacy of the approach under field contexts.
Research sample	Ivermectin efficacy was tested on <i>Anopheles coluzzii</i> mosquitoes. The mosquito colony was established from mosquitoes caught in the wild in the study region. This species is opportunistic and feeds on animals and humans and is a major malaria vector in the region. Cattle crossbreed Soudaneese Fulani Zebu x Baoulé Taurine was selected because it represents the major breed in this same region of Burkina Faso. Soil samples were collected in the same area and represent a variety of Burkinabé agricultural soils.
Sampling strategy	Seven cattle per experimental arm plus reserve cattle (as hosts for the sampled mosquitoes) were the maximum holding capacity of the research stable, allowing to take into account potential cattle effects. The resulting number of mosquito data (40 mosquitoes per cattle and time point) were considered from previous study experience to be a sufficient sample size for this descriptive study to assess ivermectin efficacy. The resulting sampling scheme for pharmacokinetic data represented a feasible scope for the chemical analysis with our established methods. The number of soil samples was selected from previous experience and relied on approval of farmers to allow sampling on their fields.
Data collection	Plasma, dung, and mosquito samples were collected and processed by Lamidi Zéla and Sié Hermann Pooda with assistance from the CIRDES technical team. Soil samples were taken and processed by Daniel Frank Kaiser with assistance from Sié Hermann Pooda and Andre Patrick Heinrich. Chemical analysis of ivermectin was performed by Andre Patrick Heinrich and Alexandra Schinzel, assisted by technical staff and students.
Timing and spatial scale	Plasma, dung, and mosquito samples were collected from April-December 2019 for up to 21 instances. Soil samples from 30 fields were collected in late October 2019 in three villages, located around 80 km from Bobo-Dioulasso where the cattle were kept. Villages were clustered in a radius of approximately 20 km. Chemical analysis was performed starting in March 2020.
Data exclusions	No data were excluded from the presented analyses.
Reproducibility	Mosquito samples for each time point represent clusters of 4x10 mosquitoes per cattle. Each plasma or dung sample was divided into two technical replicates which were extracted and measured individually. All experimental procedures were based on established, tested protocols. All details on procedures in the manuscript and Supplemental information will allow to reproduce the experiments. We did not attempt to repeat the experiment.
Randomization	Cattle were randomly assigned to the experimental arms and to a place in the stable using a random number generator in MS Excel. Seven cattle per experimental arm were used for efficacy data and considered as random in the statistical modeling. Mosquitoes exposed to cattle were for every exposure time point subsamples from different mosquito breeding cages which were mixed to

increase variability. The location of exposure cages (four cages, containing ten mosquitoes each per cattle) in the insectary for mortality follow-up was random. Chemical analysis of ivermectin in dung and plasma was partially randomized in groups of 10-20 consecutive samples per analysis at once.

Blinding

Blinding was not considered necessary for the scope for this study.

Did the study involve field work?

☒ Yes ☐ No

Field work, collection and transport

Field conditions

Thirty fields, clustered in different groups, were sampled in three villages in southwestern Burkina Faso in late October 2019. Average outdoor temperatures are provided in Supplementary Table 11.

Location

Coordinates of all sampled fields are provided in the Supplementary Information (Methods and Data) file and on a map in the main manuscript.

Access & import/export

The fields for the soil sampling campaign were pre-selected by local agricultural technicians who informed field owners about the process. Final choice depended on the permission of farmers who volunteered to allow sampling on their fields. Soil sample material from Burkina Faso was imported to Germany under clearance provided by the RP Gießen, Pflanzenschutzdienst under Directive 2008/61/EC, issued in document no. 2019/539925, endorsed by the Direction de la Protection des Végétaux et du Conditionnement (DPVC), Burkina Faso.

Disturbance

Field owners were informed about the intended soil sampling on their fields which was only undertaken with their approval.

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Materials & experimental systems

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☒ ☐ Antibodies

☒ ☐ Eukaryotic cell lines

☒ ☐ Palaeontology and archaeology

☐ ☒ Animals and other organisms

☒ ☐ Clinical data

☒ ☐ Dual use research of concern

Methods

n/a Involved in the study

☒ ☐ ChIP-seq

☒ ☐ Flow cytometry

☒ ☐ MRI-based neuroimaging

Animals and other research organisms

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Laboratory animals

Cattle were of crossbreed Soudaneese Fulani Zebu x Baoulé Taurine and were kept in a net-protected stable at the Centre International de Recherche-Développement sur l'Élevage en zone Subhumide (CIRDES), in Bobo-Dioulasso, Burkina Faso. At the beginning of the study, average cattle age was 3 years, and average cattle weight was 122 kg. Information on veterinary care are provided in the manuscript, and data on cattle weight gain in the Supplementary Data file.

Wild animals

For the established *Anopheles coluzzii* mosquito colony, wild blood-fed females were collected in dwellings of the Kou Valley, 50 km northwest of Bobo-Dioulasso in southwestern Burkina Faso (decimal degrees 11.387222, -4.411667), between February and March 2019. At the start of the experiments, mosquitoes were 2 months old. The colony was kept in the insectary of CIRDES in collaboration with the Institute de Recherche en Sciences de la Santé (IRSS).

Reporting on sex

Cattle involved in the study were all male from the same crossbreed. This was done to avoid sex-confounding effects on mosquito survival and ivermectin pharmacokinetics, and to avoid accidental treatment of gestating cattle.

Field-collected samples

Cattle plasma and dung samples were collected in the stable as described in the main manuscript.

Ethics oversight

The study received approval from the CIRDES ethical committee under letter N°15/CE-CIRDES/16-10-2018.

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