I2I Landscaping exercise

Clinical trials for endectocides.

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Abbreviations

3D	Three dimensional
AI	Active ingredient
BOHEMIA	Broad One Health Endectocide-Based Malaria Intervention in Africa
CDC	Centre for Disease Control
CI	Confidence Interval
HPPD	4-hydroxyphenylpyruvate dioxygenase
IRS	Indoor residual spraying
IVM	Ivermectin
LLINs	Long-lasting insecticidal nets
MDA	Mass drug administration
MoA	Mode of action
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
SMFA	Standard membrane feeding assay
SOPs	Standard operating procedures
WHO	World Health Organisation

Terminology

Endoparasitic: Lethal to parasitic organisms inside the body, such as worms.

Ectoparasitic: Lethal to parasites outside the body, including mosquitoes, ticks.

Efficacy: The killing effect of the compound over time.

Duration of mosquito killing effect/Time under the curve: The concentration of the compound in the blood over time and how long it remains lethal to mosquitoes.

Pharmacokinetic (PK) profile: The drug-concentration in blood over time. Depends on the recommended safe dosing regimens as described by the manufacturer and food and drug administration (FDA) standards.

Pharmacodynamic (PD) profile: The compound concentration-effect curve on the target species.

Pharmacokinetic/pharmacodynamic (PK/PD) modelling: Techniques that combine the PK and PD profile of a compound to describe the lethal effect of the compound over time on the mosquito.

Hazard ratio: The likelihood of mortality compared to a control group.

Summary

Aim and key questions addressed	- Compounds that can be safely administered to humans or animals to target blood-feeding arthropods. - An impact on individual mosquito longevity can largely impact the mosquito vectorial capacity, thereby interrupting disease transmission. - Endectocides are proposed as a complementary tool alongside currently existing vector control tools for malaria.
Context	- Field administration
Test item	- Endectocidal drugs
Mosquito population	- Wild populations
Number of mosquitoes per replicate	- N/A
Endpoints measured	- The entomological effects included in the validation process for ivermectin focus on the two primary entomological outcomes: Mosquito parity and mosquito abundance
Exposure time	- N/A
Holding time	- N/A
Indicative of personal protection	- No
Suitable chemistries	- Currently no approved endectocide for malaria control, however, majority of research is based on ivermectin.
Appropriate controls	- N/A
Relevant stage of production pipeline	- N/A
Characterisation of output	- Well categorised for uses other than malaria vector control.
Accessibility	- Need for mass drug administration programmes
Cost	- Cost associated with mass drug administration programmes

Level of validation and characterisation of outputs	- Processes of validation for clinical and field trials for endectocides exist as a standard to most entomological and epidemiological field trials and are not specific to active ingredients, however this may change in the future, as trial data emerges for ivermectin.
Outstanding questions, gaps and priorities	- No official guidance has been generated from the sufficient evidence, despite numerous funding streams being dedicated to generating an evidence base. - Regardless of the outcome of the current clinical trials, the evidence generated thus far should be used as a template for other drugs to be explored in different avenues. - It is urgent to generate the evidence basis which confirms this mechanism of action is possible and epidemiological impact is achievable.
Key references, related SOPs, guidelines and publications	- I2I Landscaping exercise, Standard membrane feeding assay and PK/PD modelling for endectocides (I2I., 2023) - I2I Landscaping exercise, Endectocides overview (I2I., 2023) - Billingsley, P., Binka, F., Chaccour, C., Foy, B. D., Gold, S., Gonzalez-Silva, M., … Zulliger, R. (2020). A roadmap for the development of ivermectin as a complementary malaria vector control tool. American Journal of Tropical Medicine and Hygiene, 102(Suppl 2), 3–24. https://doi.org/10.4269/ajtmh.19-0620 - World Health Organization. (2021). Preferred product characteristics: Endectocide products for malaria transmission control

Overview

An endectocidal drug is a compound that can be safely administered to humans or animals to target blood-feeding arthropods. This tool is already being exploited in veterinary medicine to treat ectoparasites, such as ticks or fleas, in domestic and non-domestic animals and is also successfully deployed in public health to treat endoparasites, such as worms. Its impact is proposed through mass drug administration (MDA) during high transmission seasons. An impact on individual mosquito longevity can largely impact the mosquito vectorial capacity (the rate at which future infections arise from a currently infective mosquito), thereby interrupting disease transmission. Endectocides are proposed as a complementary tool alongside currently existing vector control tools for malaria.

There is currently no approved endectocide for the control of malaria and most of the research to establish an evidence base is on ivermectin, a broad-spectrum drug with an extremely well-established safety profile. Ivermectin has been used to treat onchocerciasis and lymphatic filariasis in country-wide MDA campaigns since the 1980s and has formed the cornerstone of neglected tropical disease elimination (Amazigo, 2008; Ottesen, Hooper, Bradley, & Biswas, 2008).

The initial lethal effect of ivermectin on mosquitoes was first identified in 1985 (Pampiglione, Majori, Petrangeli, & Romi, 1985) and the first controlled human study was conducted in 2010 (Chaccour, Lines, & Whitty, 2010). The application of ivermectin as an endectocide against mosquitoes for malaria control has gained much momentum since the creation of the Ivermectin Roadmappers consortium in 2017 (Billingsley et al., 2020). In 2021, the World Health Organization (WHO) announced its preferred product characteristics of an endectocidal drug, based largely on the current body of evidence on ivermectin (World Health Organization, 2021).

Recent studies have identified and established the pharmacokinetic and pharmacodynamic profile of ivermectin against Anopheles mosquitoes (Chaccour, Hammann, & Rabinovich, 2017;

Smit, Ochomo, Waterhouse, et al., 2019) which have been followed by safety and clinical trials in the field (Foy et al., 2019; Smit et al., 2018). A malaria transmission model study has simulated the potential impact on a larger scale (Slater et al., 2020; Slater, Walker, Bousema, Okell, & Ghani, 2014). The clinical trials conducted have found no epidemiological impact (Bradley, Moulton, & Hayes, 2019; Dabira et al., 2022; Foy et al., 2019) and results are pending from further trials to generate the necessary evidence to approve ivermectin as an official tool for malaria control by WHO. Other compound types, including the isoxazolines (Miglianico et al., 2018) are undergoing early investigation to define their potential as an ectoparasitic drug for malaria control, but ivermectin is widely expected to be the "first in class' endectocide.

Define Accepted Methodologies

Are there existing standard operating procedures (SOPs)/Guidelines detailing methodologies?

Currently there are no officially approved or endorsed methodologies, SOPs, or guidelines on establishing the efficacy of an endectocidal drug. The gold standard approach is the **'**standard membrane feeding assay', which has been adopted to demonstrate the efficacy of drugs/compounds to kill mosquitoes. Small scale and late-stage research have adopted this approach. Please refer to the I2I Landscaping exercise 'Standard membrane feeding assay and PK/PD modelling for endectocides', for more information.

Entomological impact

- The parity rate is widely accepted as the indicator of mosquito population longevity. Mosquito parity is the defined as the number of times a female mosquito has laid eggs and provides information on the likely age of the mosquito. Assessment of mosquito parity is performed by ovary tracheation, where-by mosquito ovaries are dissected and observed for evidence of oviposition.

- A secondary entomological endpoint is often mosquito abundance, which can be collected via many adult mosquito collection techniques, including CDC light traps, human landing catches and pyrethrum spray catches.

Epidemiological impact

- WHO has stated that it requires evidence of impact, deemed as at least a 20% reduction in clinical incidence following MDA treatment, obtained from two clinical trials of the same dosing strategy but from two varying epidemiological settings. The Broad One Health Endectocide-based Malaria Intervention in Africa (BOHEMIA) trial will begin in early 2022 and will look to develop the evidence basis for WHO approval (*Broad One Health Endectocide-based Malaria Intervention in Africa (BOHEMIA)*). The trial is being conducted in Mozambique and Tanzania and will administer single doses of 400ug/kg of ivermectin either to the human population alone or the human and livestock population, alongside the third arm of a placebo control.

Are these sufficiently detailed?

Methodologies are described in varying detail in academic research papers. Documented methods have evolved and become increasingly more detailed.

- The most detailed and described methods for this exist in the form of published academic papers and require tailoring to compound mode of action.
- Clinical trials for ivermectin as an endectocidal drug for malaria are described in detail and published at clinicaltrials.org website.

Do these methods require specialised/non-standardised equipment and/or training?

In-vivo clinical trial

- Specialised training associated with drawing blood from patients.

- Clinician and medical expertise to monitor adverse events.
- Depending on clinical and/or field trial design, the specialised equipment, facilities, and training required varies. A number of aspects required for vector control field trials are specified elsewhere (World Health Organization, 2017). Importantly, a vector control trial on a potential endectocide encompasses both a clinical and entomological aspect and as such requires huge resources and expertise.

Are there issues with the methods or their interpretation?

Demonstrating the impact of an endectocidal drug on entomological and epidemiological outcome has many challenges. As demonstrated in the variation in the epidemiological trials currently ongoing, issues in study design make it difficult to draw comparisons between trials.

- Difficulty in assessing many village clusters while also monitoring participants, vectors, and environmental factors.
- The requirement and threshold to demonstrate efficacy is extremely high.
- Difficulty in capturing all secondary effect outcomes from an intervention that is also influenced by environmental factors.

What AIs or combinations of AIs have the tests been used for?

All clinical trials into the use of a compound for an endectocide for malaria control adopt ivermectin as the active ingredient. Its status as an approved therapeutic drug for use in humans and animals enables testing within a clinical setting.

Table 1. Summary of clinical trials which use ivermectin (endectocide) for malaria control

Randomised control trial ref. No.	Country	Participants	Dates	Study arms	Primary outcome
RIMDAMAL [NCT02509481] (Foy et al., 2019)	Burkina Faso	2712	June – December 2015	Single MDA: 150 ug/kg IVM + albendazole Six MDA: (3 weeks apart) 150 ug/kg IVM + albendazole	Malaria incidence: Risk difference -0·49 [95% CI -0·79 to -0·21], p=0·0009
IVERMAL [NCT02511353]	Kenya	141	July 2015 – July 2016	Placebo: 3-day course of DP + 600ug/kg/day Placebo Intervention arm 1: 3-day course of DP + 300ug/kg/day Placebo + 300ug/kg/day Ivermectin Intervention arm 2: 3-day course of DP + 600ug/kg/day Ivermectin	Mosquito survival 14 days after feeding on blood taken from study participants on day 7 after taking regimen.
REACT [NCT03074435]	Burkina Faso and Cote d'Ivoire	18,000	April 2016 – April 2019	Five arms: -Control -Insecticidal paint -Larvicides -Ivermectin: injectable doses given to peri-domestic animals	Malaria incidence over two consecutive years

				-Information, education, communication	
MASSIVE [NCT03576313] (Dabira et al., 2022)	The Gambia	10,638	Aug-Oct 2018 July-Sept 2019	3 x IVM (300-400ug/kg) + DP Control: Standard malaria control interventions. [Over 3 months]	Prevalence of malaria infection (PCR) [Over 12 months] OR:0.3 (p<0.001) Vector parity rate [7-14 days after drug administration] No effect on parity rate
MATAMAL [NCT04844905]	Guinea-Bissau	24,000	May 2021 – August 2023	3 x 300-400ug/kg IVM + DP 3 x 300-400ug/kg Placebo + DP [Over 3 months]	Malaria Plasmodium prevalence over two years
RIMADAL II [NCT03967054]	Burkina Faso	4,088	July 2019 – July 2023	3 x 300ug/kg IVM 3 x 300ug/kg Placebo (SCP drugs given on the same day) [Over 4 months]	Malaria incidence (timeframe up to 8 months)
BOHEMIA [NCT04966702]	Tanzania, Mozambique	100,000	Jan 2022 - March 2023	IVM 400ug/kg once per month for 3 months IVM (to Humans + Livestock) 400ug/kg once per month for 3 months Livestock: injectable ivermectin at 1% will be used. Control (Albendazole) 1 dose per month for 3 months	Safety and efficacy Malaria incidence [6 months follow-up]

Are they validated, for which AIs/entomological effects, and to what extent?

Processes of validation for clinical and field trials for endectocides exist as a standard to most entomological and epidemiological field trials and are not specific to active ingredients, however this may change in the future, as trial data emerges for ivermectin. The entomological effects included in the validation processes focus on the two primary entomological outcomes: Mosquito parity and mosquito abundance.

Methods of clinical trial validation include:

- Baseline entomological surveys
- Control arms as a comparator against intervention arms
- Standardisation of village and participant characteristics
- Selection of villages or clusters randomised
- Inclusion of spillover zones to adjust for residual effects
- Equipment validation processes, e.g., insecticide resistance tests
- Drug/compound/active ingredient authentication

In trial data analysis

- Cluster adjusted analysis
- Adjustment for confounding variables
- Adjustment for systematic error (bias) and random error
- Randomisation, allocation concealment, blinding and sample size factors should be included

What inputs need to be characterised? e.g., samples, mosquitoes, equipment

Input parameters for a clinical trial of an endectocide depends on the trial design and have been described elsewhere in published trial methodologies (Described in table 1). An example of inputs to be describe for such a trial include:

– Study/trial research questions (aims and objectives)

- Study design
- Intervention and control arms
- Study size
- Dosing regimen
- Study population
- Intervention and control villages
- Study time and length of follow-up
- Primary and secondary outcomes
    - Entomological
    - Epidemiological
    - Safety
    - Other
- Effectiveness/Efficacy endpoints

Are endpoints clearly defined and appropriate? Who were they defined by?

The methods described have been obtained from academic research, defined early on by researchers. The endpoints for clinical trials for an endectocide are established but are yet to be validated.

- The difference in mosquito parity between intervention and control arms.
    - Debate exists around the appropriateness of mosquito parity as a measurement of longevity; however, it is used as an entomological outcome indicator in numerous vector control trials.
- Entomological outcomes of abundance, as determined by clinical trials on ivermectin.
- Epidemiological outcomes
    - Clinical incidence – under 5's
    - Clinical incidence – All age
- The appropriateness of outcomes will become clearer as data clinical trial data emerges.

Are there supporting SOPs? e.g., cleaning SOPs, mosquito rearing SOPs required

- Published methodologies are described for all planned and ongoing clinical trials for ivermectin.
- SOPs exist for the for assessment of novel vector control tools and the design of field trials.

Define Current Use Practices

Does everybody use the same SOP?

- No official defined methodology is currently available.
- Clinical trials on ivermectin differ to some extent, depending on the research objective.
- Primary and secondary outcomes can be uniform between clinical trials, however, methods used to obtain them can differ.
- Information on optimal vector control trial methods is available but can differ between studies and research groups according to factors such as research objective or budget.

Are there differences of interpretation of the method?

Since no defined methodology is available and no approved compound exists, varying interpretations can exist. Varying clinical trial designs demonstrate varying interpretations of how to define the efficacy of an endectocidal compound, although many trial designs can be determined by field site or availability of resources and funds.

Are the results obtained largely consistent between studies?

Very little studies have been conducted on potential endectocides to date, however the defined killing effect outcome (LC50) is largely uniform between studies for ivermectin. No identical clinical or field trials have been performed for ivermectin. The outcomes between the completed clinical trials are consistent in demonstrating no impact of epidemiological outcome ($p>0.001$).

Currently, two study areas are replicating an identical trial design for ivermectin (The BOHEMIA trial).

Is further development, refinement or validation of the method required? Based on priority, significance, and relevance of method.

Areas of further development required

- Official defined protocols for the assessment of endectocidal compounds can streamline and optimise future research.
- A better understanding of the full epidemiological effects of reducing mosquito longevity way are required.

Identify Potential Sources of Variation

What are the sources of variability in the method, and are their means to minimise or characterise these?

As demonstrated by the large variation in clinical trials in the field to date, huge sources of variability exist in the generation of evidence of the impact of an endectocidal drug. Differences in study design have been the source of variability in results obtained thus far.
However, no effect on the primary entomological outcome of mosquito parity was found and no effect could be attributed to ivermectin, due to it being co-administered with DP (Dabira et al., 2022). In the RIMDAMAL trial malaria incidence was reduced in the intervention arm (risk difference of -0.49) (Foy et al., 2019). However, a separate follow-up analysis of trial data subsequently found, that when taking clustering into account, no difference in malaria incidence between the control and study intervention existed (Bradley et al., 2019). A recently published Cochrane review found no studies have demonstrated the effect of ivermectin as a vector control tool to control malaria (de Souza et al., 2021).

Do current method/s need to be adapted for new active ingredients/MoA/types of tools?

- The safety profile of the compound will determine the methodologies adopted in a clinical and/or field setting.

Are new methods required? Identify areas where current method/s are not suitable or sufficient.

- Improving the design of large-scale clinical trials in the field to ensure that the study is powered to detect the additional effect of ivermectin. Placing more emphasis on study design for vector control tools enables trials to have the ability to generate the necessary evidence using the resources available.
- Other experimental designs may include administering small animals with known doses of a drug and feeding wild populations on such animals, however additional ethical processes must be in place for such procedures.

Gaps in biological or other understanding that hinder method development or validation

- Lack of available and safe drugs that could easily fulfil the safety requirements for MDA.
- Current gaps in the pharmacological profiles of animals, such as cattle could be obtained in order to identify the predicted drug blood concentration of an endectocidal compound.

Prioritisation – is there an issue that needs to be addressed, what specifics, how urgent is the need?

The first evidence that ivermectin was lethal to mosquitoes was generated four decades ago and yet still no official guidance has been generated from the sufficient evidence, despite numerous funding streams being dedicated to generating an evidence base. The momentum such as that generated by the "ivermectin roadmappers" has no doubt accelerated and streamlined the research evidence basis for ivermectin, however, the timing is not sufficient when considering the current WHO trajectory for malaria case and death estimates. Multiple sources agree that urgent action is necessary and novel methods are an essential component of vector control. Regardless of the outcome of the current clinical trials, the evidence generated thus far should be used as a template for other drugs to be explored in different avenues.

Lack of evidence basis

The lack of evidence that defines the impact of a human/animal therapeutic drug as an endectocide on malaria outcomes is a severe hindrance to any future research on potential endectocidal compounds. To set a precedent, it is urgent to generate the evidence basis which confirms this mechanism of action is possible and epidemiological impact is achievable.

Flawed study design of large clinical trials

Key to the success of generating an evidence base is the study design of trials. Clinical trials that may have demonstrated an impact of ivermectin have not had the ability to detect the additional impact due to missing control arms. Ensuring an appropriate study design is adopted prior to implementation is key to building the necessary evidence base for this strategy of vector control.

Emphasis on the potential of an endectocide for animals

Due to the extremely high safety barrier associated with mass administering drugs to human populations and the much lower threshold in veterinary medicine, the opportunity to exploit the

potential of dosing animal populations should be further explored. Only two of the seven clinical trials have included the use of animal dosing in their study design. Areas with zoonotic transmission of malaria can provide an opportunity for such research. Animals like cattle can be dosed much higher than humans (Due to larger a larger body mass, but also due to a reduced safety barrier), enabling higher drug blood concentrations to be obtained, which would enhance this vector control tool further.

Techniques to discern the age structure of a population as a measure of success

The outcome of vector parity used as a primary indicator of the measure of this vector control tool is a labor-intensive indicator to obtain. A number of novel mosquito age-grading techniques have been developed. However, as they are not close to development for practical or economic use in the field thus far. Such tools, when available, could accelerate the validation process of a strategy such as an endectocide.

Utilising the drug repurposing trajectory

The role of repurposed drugs in public health is increasing. A potential screening programme could address this, whereby mass-scale drug screening could identify appropriate candidates. The way to establish a potential endectocide would be to focus on a drug that already has an established safety profile since this aspect would prove the most difficult to address in future research.

Prioritising the acceptability rate

The social aspect of this strategy is vital in its success since adherence is vital. To convince entire regions of underserved malaria endemic communities to take a drug that offers no direct benefit requires a large social component to studies and attention in areas where access to healthcare is very poor.

Official standardization of protocols

Protocols for assessing novel compounds requires standardisation and publication by the relevant assessment bodies. Preferred attributes should be defined by assessment bodies, by which researchers and academics can assess compound efficacy. There is an urgent need for a streamlined approach for the assessment of endectocidal compounds, despite the complexities of identifying and assessing the efficacy of such a compound.

Discerning the potential role of biotechnology in an endectocide

Much of the mosquito killing effect data from ivermectin suggests its toxicity is time limited. The use of slow-release capsules has been trialed, but this research should be accelerated and trialed for other compounds that have demonstrated early potential. In addition, the cost effectiveness of this should also be considered.

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