Title	**1686A - Pharmacokinetic and Pharmacodynamic Modeling for the Prediction of the Mosquitocidal Effect Duration of High-Dose Ivermectin (The IVERMAL PK/PD Model)**
Session	Session Young Investigator Award Session E
Authors	**Menno R. Smit**[1], Eric O. Ochomo[2], David Waterhouse[1], Titus K. Kwambai[3], Bernard O. Abong'o[2], Teun Bousema[4], Nabie M. Bayoh[5], John E. Gimnig[5], Aaron M. Samuels[5], Meghna R. Desai[5], Penelope A. Phillips-Howard[1], Simon K. Kariuki[2], Duolao Wang[1], Feiko O. ter Kuile[1], Steve A. Ward[1], Ghaith Aljayyoussi[1] [1]Liverpool School of Tropical Medicine, Liverpool, United Kingdom, [2]Kenya Medical Research Institute (KEMRI), Kisumu, Kenya, [3]Kenya Ministry of Health, Kisumu, Kenya, [4]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [5]U.S. Centers for Disease Control and Prevention, Atlanta, GA, United States
Abstract	It was recently shown that the mosquitocidal effect on *Anopheles gambiae s.s*. populations feeding on malaria patients treated with high-dose ivermectin lasts for at least 28 days after the start of ivermectin administration when co-administered with 3 days of dihydroartemisinin-piperaquine (DP). The current pharmacokinetic and pharmacodynamic analysis aimed to determine whether a drug interaction or an unidentified ivermectin metabolite could be contributing to the prolonged mosquitocidal effect of ivermectin. In the main trial, 141 adults with uncomplicated malaria were randomly assigned to receive ivermectin 0, 300, or 600 mcg/kg/day for 3 days. During 28 days of follow-up, 1,393 venous plasma samples were collected. Paired mosquito incidence rates for death (IDR) during 14-days post-feeding were available for 850 time points. Following liquid-liquid extraction, ivermectin concentrations were measured using liquid chromatography-mass spectrometry (LC-MS). Pmetrics® 1.5.0 was used for the population modelling of both PK and PD data. Ivermectin concentrations were above the lower limit of quantification (LLOQ: 5 ng/mL) for 534 time points, of which 246 had paired IDR's. The population pharmacokinetics of ivermectin were best described by a two-compartment oral absorption model. Based on the PK/PD model there was a consistent association between (1) predicted and observed ivermectin concentrations and (2) predicted ivermectin concentrations and observed mosquitocidal effect throughout the entire duration of the study (28 days). The half maximal effective concentration (EC50) for incidence rate of death by day 14 was 17.1 ng/mL (IQR 15.1, 19.1). Predicted median concentrations remained mosquitocidal for at least 28 days. The PK/PD model accurately predicted mosquitocidal activity for the entire duration of the study (28 days) without the need to invoke unidentified variables such as an active metabolite. (ClinicalTrials.gov: NCT02511353)
Venue(s)	November 5, 2017, 12:20 - 12:35 PM, Convention Center - Room 337/338 (Level 300) November 5, 2017, 10:00 - 3:00 PM, Convention Center - Room 331/332 (Level 300) November 8, 2017, 12:00 - 1:45 PM, Convention Center - Hall F and G (Level 100)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/4630 http://www.abstractsonline.com/pp8/#!/4395/presentation/4519
MT link	http://www.malariaeradication.org/mesa-track/efficacy-and-safety-high%E2%80%90dose-ivermectin-reducing-malaria-transmission-ivermal

Title	**High-Dose Ivermectin for Malaria Elimination: A Dose-Finding Study (IVERMAL Study, Kenya)**
Session	Session 74 - Ivermectin and Mosquitoes: The Vital Role of Pharmacokinetics and Pharmacodynamics
Authors	Menno Smit *Liverpool School of Tropical Medicine at KEMRI/CDC, Kisumu, Kenya*
Abstract	-
Venue(s)	November 7, 2017, 10:30 - 10:45 AM, Convention Center - Ballroom II (Level 400)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/4654
MT link	http://www.malariaeradication.org/mesa-track/efficacy-and-safety-high%E2%80%90dose-ivermectin-reducing-malaria-transmission-ivermal

Title	**145 - Ivermectin inhibitory effects on zika virus and chikungunya virus infection**
Session	Session 28 - Poster Session A: Presentations and Light Lunch
Authors	**Taweewun Hunsawong**[1], Jindarat Lohachanakul[1], Sarunyou Chusri[2], Butsaya Thaisomboonsuk[1], Kathryn B. Anderson[1], Alden L. Weg[1], Louis R. Macareo[1], Damon W. Ellison[1] *[1]USAMD-AFRIMS, Bangkok, Thailand,* *[2]Faculty of Medicine, Prince of Songkla University, Songkla, Thailand*
Abstract	Zika virus (ZIKV) and chikungunya virus (CHIKV) are co-circulating in many countries including Thailand. Both viruses are transmitted to humans through the bite of *Aedes* mosquitoes. Outbreaks of these viruses have sporadically occurred and there are no vaccines or anti-viral treatments available for either of these potentially devastating diseases. Ivermectin is an anti-parasitic drug which is approved for use in humans at a concentration of 150-200 µg/Kg which has been shown in pharmacokinetic studies to correspond to serum concentrations in humans of 7-95 ng/ml. In this study, we investigated the potency of ivermectin to inhibit ZIKV (Asian genotype: SV127/14) and CHIKV (Vaccine strain clone 181) infections *in-vitro.* Two mammalian cell lines (vero and LLC-MK2) and a mosquito cell line (C6/36) were treated with various concentrations of ivermectin and inoculated with ZIKV or CHIKV at MOI of 0.1. We found that ivermectin was able to reduce the number of plaques of ZIKV and CHIKV in both cell types. No impact on cytopathic effect in LLC-MK2 and C6/36 cell lines was observed but an inhibitory effect during virus penetration/replication was seen in both mammalian and mosquito cell lines. Importantly, the half maximal inhibitory concentration (IC50) of ivermectin for ZIKV (618 ng/ml) and CHIKV (2,360 ng/ml) infections in vero cells would fall within the range of serum concentrations previously deemed to be safe by the Food and Drug Administration for mass-drug administration for parasitic infections. These data suggest that ZIKV is more sensitive to ivermectin than CHIKV. The results from this study indicate a potential use for ivermectin as a treatment option for ZIKV and CHIKV.
Venue(s)	November 6, 2017, 12:00 - 1:45 PM, Convention Center - Hall F and G (Level 100)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/2895
MT link	-

Title	**Ivermectin for malaria in Southeast Asia (IMSEA Study, Thailand)**

Session	Session 74 - Ivermectin and Mosquitoes: The Vital Role of Pharmacokinetics and Pharmacodynamics
Authors	Kevin Kobylinski *Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand*
Abstract	-
Venue(s)	November 7, 2017, 10:15 - 10:30 AM, Convention Center - Ballroom II (Level 400)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/2688
MT link	http://www.malariaeradication.org/mesa-track/open-label-study-evaluate-safety-tolerability-potential-pharmacokinetic-interactions-and

Title	**Single-dose ivermectin tablet: a new paradigm**
Session	Session 74 - Ivermectin and Mosquitoes: The Vital Role of Pharmacokinetics and Pharmacodynamics
Authors	Jose Muñoz *IS Global, Barcelona, Spain*
Abstract	-
Venue(s)	November 7, 2017, 10:45 - 11:10 AM, Convention Center - Ballroom II (Level 400)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/2689
MT link	-

Title	**Modelling the impact of high-dose ivermectin on malaria transmission**
Session	Session 74 - Ivermectin and Mosquitoes: The Vital Role of Pharmacokinetics and Pharmacodynamics
Authors	Hannah Slater *Imperial College London, London, United Kingdom*
Abstract	-
Venue(s)	November 7, 2017, 11:35 - 12:00 PM, Convention Center - Ballroom II (Level 400)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/2691
MT link	http://www.malariaeradication.org/mesa-track/modelling-understand-potential-impact-ivermectin-malaria-transmission
Title	**1065 - Modelling the potential of ivermectin treated cattle as a novel malaria vector control tool: implications of killing zoophilic mosquitoes**
Session	Session 86 - Poster Session B: Presentations and Light Lunch
Authors	**Amy Dighe**, Azra Ghani, Hannah Slater *MRC Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom*
Abstract	Current malaria vector control interventions target anthropophilic, indoor-biting mosquitoes, leaving zoophilic, exophilic vectors to sustain residual transmission of malaria, even in areas with high vector control coverage. It has been suggested that targeting zoophilic vectors by injecting cattle with the multi-purpose mosquitocidal drug ivermectin (IVM) could ameliorate this. However, applying such a strong selection pressure against zoophilic vectors could shift vector populations towards being more anthropophilic which would increase the human biting rate. Here, a mathematical model of vector dynamics and malaria transmission are linked with an existing ecological larval model and extended to simulate administration of IVM to cattle. When this framework is used to investigate the effects of this intervention in a homogenous

	vector population of mosquitoes with identical Human Biting Indexes (HBIs), the administration of an annual dose of IVM to cattle is predicted to considerably reduce malaria infection, particularly when given immediately prior to the peak of the rainy season in a seasonal transmission setting. However, if two competing species with different HBIs are present, the intervention may cause an increase in annual malaria infections by changing the composition of the vector population to include a larger proportion of anthropophilic mosquitoes. If the two vector species occupy entirely overlapping breeding sites (complete competition), a single dose of IVM is predicted to cause a permanent increase in malaria prevalence. In reality, competition is more likely to be partial, in which case a single dose of IVM is predicted to only increase malaria prevalence temporarily when the level of competition is above a certain threshold. These findings highlight the importance of considering the local vector species before planning administration of IVM to cattle.
Venue(s)	November 7, 2017, 12:00 - 1:45 PM, Convention Center - Hall F and G (Level 100)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/3637
MT link	

Title	**977 - Boosting ivermectin for vector control: cytrochrome-P-450/ABC-transporter inhibition synergizes ivermectin and increases the mortality of *Anopheles gambiae***
Session	Session 86 - Poster Session B: Presentations and Light Lunch
Authors	**Carlos J. Chaccour**[1], Marta Alustiza[2], Brian B. Tarimo[3], Helena Martí[1], José L. Del Pozo[4], Marta Maia[5] [1]*ISGlobal Barcelona Institute for Global Health, Barcelona, Spain,* [2]*Universidad de Navarra, Pamplona, Spain,* [3]*Ifakara Health Institute, Bagamoyo, Tanzania, United Republic of,* [4]*Clínica Universidad de Navarra, Pamplona, Spain,* [5]*KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya*
Abstract	Insecticide resistance and mosquito behavioural adaptations that allow avoidance of home-centred vector control measures are two of the major challenges faced by the malaria community today. In this context, the mass use of drugs that can kill mosquitoes feeding on treated subjects has potential to become a new paradigm for vector control. Ivermectin is one of the leading candidates given its excellent safety profile. In the phase of the challenge posed by insecticide resistance, a thorough understanding of the mosquito metabolic pathways and potential defence mechanisms from ivermectin is of paramount importance for vigilance purposes and early assessment if this novel strategy is to be used in the field. Simple synergistic bioassays have been previously used to identify metabolic resistance in Anopheles adults and larvae. We have conducted a synergistic bioassay to evaluate the potential involvement of ABC transporters and cytochrome P450 in the metabolism of ivermectin in Anopheles gambiae. Mosquitoes were membrane fed with matched pairs of blood samples containing the same ivermectin concentration with or without Ketoconazole (a dual cytochrome-P450/ABC-transporter inhibitor). Mosquitoes in the ivermectin plus ketoconazole group had a significantly reduced mean survival and time to median mortality as assessed by Kaplan-Meier analysis. Our results show that pharmacological inhibition of P450 and ABC transporters could further improve the efficacy of ivermectin as a vector control tool and extend the spectrum towards less susceptible vectors.
Venue(s)	November 7, 2017, 12:00 - 1:45 PM, Convention Center - Hall F and G (Level 100)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/3549
MT link	-

Title	**1470 - Investigating endectocide use in livestock as a tool to help eliminate residual malaria in Central America**
Session	Session 145 - Poster Session C: Presentations and Light Lunch
Authors	**Jefferson A. Vaughan**, Staci M. Dreyer, Kelsey J. Morin *University of North Dakota, Grand Forks, ND, United States*
Abstract	In Central America, malaria has been reduced using indoor insecticide spraying and insecticide-treated bed nets. But these tactics may not eradicate malaria because they rely on certain behavioral traits of the *Anopheles* vector - e.g., entering houses at night to feed and rest. Much of the malaria transmission in Central America occurs outdoors by *Anopheles* species that are as likely to feed on non-humans as humans (=zoophagic). To address this issue, additional tactics need to target these behaviors. Livestock management may hold the key. Our project examines the potential of endectocides to help reduce zoophagic *Anopheles* populations and eliminate residual transmission of malaria in Central America. Endectocides are chemicals widely used in the livestock industry to control intestinal nematodes and ticks. The most widely-used endectocide, ivermectin, has been shown to reduce the survival and fecundity of several *Anopheles* species when ingested in a bloodmeal. Ivermectin is increasingly important for vector control in Africa. We compared the dose-responses to ivermectin between the Central American vector, *A*. (*Nyssorynchus*) *albimanus*, and the Asian vector, *A*. (*Cellia*) *stephensi.* Toxicity of ingested ivermectin in *A. albimanus* (oral IC-50=1,349 mg/ml) was significantly less than in *A. stephensi*(oral IC-50=11 mg/ml) and far exceeded the normal range of ivermectin plasma concentration typically found in treated cattle (20-50 ng/ml). Ivermectin was 10x more toxic when injected into the thorax of *A. albimanus* (parenteral IC-50=100 ng/ml), but was still less toxic than when injected into *A. stephensi* (parenteral IC-50=16 ng/ml). This suggests that ivermectin is not readily absorbed across the gut in *A. albimanus*, and that the molecular targets of ivermectin (i.e., glutamate-gated chloride channels) in *A. albimanus* are more resistant to the effects of ivermectin than are those in *A. stephensi*. Another related endectocide, abamectin, proved much more toxic to *A. albimanus* (oral IC-50=107 ng/ml) than ivermectin. Thus, abamectin may be a better choice of endectocide to reduce zoophagic vector populations in Central America.
Venue(s)	November 8, 2017, 12:00 - 1:45 PM, Convention Center - Hall F and G (Level 100)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/3960
MT link	http://www.malariaeradication.org/mesa-track/endectocide-use-livestock-tool-help-eliminate-malaria-central-america

Title	**1746 - HPLC-Fluorescence Method for Detection of Ivermectin in Mosquito Blood Meals**
Session	Session 145 - Poster Session C: Presentations and Light Lunch
Authors	**Chilinh Nguyen**, Brian D. Foy *Colorado State University, Fort Collins, CO, United States*
Abstract	Ivermectin (IVM) is an endectocidal drug that can be lethal to many biting arthropod vectors, including mosquitoes. We have been developing IVM mass drug administrations (MDA) as a tool for integrated malaria control due to its effect on *Anopheles* mosquitoes when they bite IVM-treated people, and as a control method for West Nile virus transmission due to its effect on *Culex tarsalis* when they bite birds given IVM-treated feed. While IVM has been shown to be toxic to these species, IVM

	detection and quantification in mosquito blood meals has not been published. This is important as IVM pharmacokinetics is studied using venous-drawn serum or plasma samples, however, given the highly lipophilic nature of IVM, mosquitoes may be ingesting a different amount of IVM from subdermal capillaries as they are often in close proximity to subdermal fat deposits. *An. gambiae* were fed serial dilutions of IVM in artificial blood meals at concentrations of 50, 25, 12.5, 6.25, 3.125, and 1.56 ng/ml and frozen at 0 hr and 12 hr post blood meal. IVM was detected at the lowest blood meal concentration of 1.56 ng/ml at both time points in individual blood fed *An. gambiae* using HPLC-fluorescence methods. This represents a potential ability to detect IVM in *Anopheles* caught resting in houses after blood feeding on treated humans the previous night, and IVM serum concentrations that can be found in humans at least a week following MDA for onchocerciasis control. Our method was also able to detect IVM in individual *Cx. tarsalis* given an artificial blood meal of 25 ng/ml and held for either 0 hr or 20 hr post-blood feed. Future experiments will include determining the limits of quantification and analyzing *in vivo* IVM blood meals of *Cx. tarsalis* from birds and *An. gambiae* from humans. This method could be used to determine IVM coverage within mosquito populations following IVM application to hosts, and could provide a critical link in understanding mosquito mortality dynamics in relation to IVM pharmacokinetics in humans and birds. This could contribute to a better understanding of the use of IVM for integrated vector control.
Venue(s)	November 8, 2017, 12:00 - 1:45 PM, Convention Center - Hall F and G (Level 100)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/4236
MT link	-

Title	**1949 - Targeting cattle for malaria elimination: marked reduction of *Anopheles arabiensis* survival for over six months using a slow-release ivermectin formulation**
Session	Session 175 - Malaria: Mosquito Transmission and Interruption
Authors	Kija Ng´habi[1], Gloria Abizanda[2], Marta Alustiza[2], Gerry Killeen[1], Fredros Okumu[1], **Carlos J. Chaccour**[2] [1]*Ifakara Health Institute, Ifakara, Tanzania, United Republic of,* [2]*Universidad de Navarra, Pamplona, Spain*
Abstract	Behavioural plasticity has allowed malaria vectors to avoid home-centered vector control strategies such as, Indoor residual spraying and insecticide-treated nets which are both remarkably effective and affordable. This unsuppressed large population is now responsible for residual malaria transmission, a major challenge in elimination efforts. Partial zoophily is the key factor in residual malaria transmission as evidenced by large proportion of mixed cattle and human blood meals in a number of vector species. Mosquitoes that feed on peridomestic livestock tend to avoid contact with insecticides, reproduce and survive to continue transmission once human blood is available again. Modelling shows that targeted use of veterinary endectocides (drugs that kill mosquitoes feeding on treated subjects) could result in incremental transmission reduction after roll-out of long-lasting insecticidal nets, indoor residual spraying and other core vector control tools. Veterinary endectocides hold potential to become a complementary strategy for malaria elimination. We conducted a trial of a long-lasting, implantable veterinary formulation of ivermectin that can sustain mosquito-killing levels of this drug for more than months. 3 calves were randomly assigned to be implanted with five silicon rods or nothing as control. 50 *Anopheles arabiensis* (triplicates) females were fed on their flanks every 2 weeks. Mosquito mortality was then assessed by counting and removing the dead for 10 days. Our results

	show a marked and significant reduction in *Anopheles arabiensis* survival that does not decay in magnitude even six months after implantation. Slow release ivermectin formulations could complement on the success achieved by home-centered measures and aid malaria elimination.
Venue(s)	November 9, 2017, 8:45 - 9:00 AM, Convention Center - Ballroom II (Level 400)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/2342
MT link	-

Title	**1950 - Investigating the Activity of the Macrocyclic Lactones Ivermectin & Moxidectin against malaria vectors**
Session	Session 175 - Malaria: Mosquito Transmission and Interruption
Authors	**Cielo Pasay**[1], Paul Mills[2], Milou Dekkers[3], Romal Stewart[4], Leon Hugo[4], Oselyne Ong[4], Chen Wu[4], Greg Devine[4], James McCarthy[1] [1]*Clinical Tropical Medicine, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia,* [2]*School of Veterinary Science, University of Queensland, Gatton, Queensland, Australia,* [3]*Queensland Animal Science Precinct, University of Queensland, Gatton, Queensland, Australia,* [4]*Mosquito Control Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia*
Abstract	Livestock that live in close proximity to human hosts are alternative blood sources for many malaria vector mosquito species. In such areas, treating peri-domestic animals with insecticides such as ivermectin or moxidectin may reduce the mosquito population, hence reduce transmission of malaria. Moxidectin has the theoretical advantage of increased lipophilic properties & longer half life. The aim of this study was to investigate the efficacy of these two macrocyclic lactones with known activity against arthropod ectoparasites. Activity was tested against the dominant malaria mosquito vector in Oceana, namely *Anopheles farauti*. Initially, activity of these drugs was tested against colony mosquitoes by membrane feeding assays where the drugs were prepared in the blood meals. Drug levels were measured in the plasma & red cell compartments in the blood meals & IC_{50} & IC_{90} levels determined. Subsequently, *in-vivo* efficacy was investigated by conducting a clinical trial where pigs were treated with ivermectin & moxidectin in doses appropriate for human administration. Then *An farauti* mosquitoes were allowed to feed on the pigs. Drug levels in the skin & blood of the pigs & mosquito mortality were monitored. Results of both the in *vitro* & *in vivo* experiments will be presented. Results of this study will assist in evaluating the potential of an innovative malaria control strategy utilising domestic animals for mosquito vector control applicable in the field setting.
Venue(s)	November 9, 2017, 9:00 - 9:15 AM, Convention Center - Ballroom II (Level 400)
URL	http://www.abstractsonline.com/pp8/#!/4395/presentation/2343
MT link	-