and cadherins. Decreased expression of extracellular matrix proteins (ECM), vitronectin, fibronectin, collagen and endothelins indicated defects in ECM and decreased tensile strength of the tissue. IL8 signaling was a highly down-regulated pathway, which together with the ECM changes, would lead to impaired neutrophil recruitment, transmigration, and activation. Pathways involved in Leishmania killing, including production of nitric oxide and NFkB signaling were also represented in 2 of the top 10 canonical pathways that were inhibited. Transcript expression was compatible (Z<-2.0) with impaired tissue repair and healing (decreased angiogenesis, lymphangiogenesis, endothelial cell development and connective tissue differentiation). In contrast, functions predicted to be activated (Z>2.0) indicated tissue damage (mediated by upstream gene regulators IFNγ, TNFα and CxCL10), bleeding (by coagulation system defects), dysgenesis, and edema. Collectively these data indicate that impaired splenic tissue organization and repair is likely to be part of the pathogenesis of human VL.

1403

CHAGAS DISEASE-INDUCED FUNCTIONAL PERTURBATIONS OF THE GASTROINTESTINAL MICROBIOME

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Chagas disease is a tropical disease endemic to Latin America, caused by infection with *Trypanosoma cruzi* parasites. Six to seven million people are *T. cruzi*-positive, thirty to forty percent of which will develop cardiac symptoms, including arrhythmias, aneurysms and fatal heart failure. A minority of patients will develop gastrointestinal manifestations (megaoesophagus and megacolon), alone or in combination with cardiac symptoms. Gastrointestinal tissues are also a major site of chronic parasite persistence, in mouse models of disease, and may serve as reservoir for cardiac re-seeding following unsuccessful treatment. However, the pathogenesis of gastrointestinal Chagas disease is still poorly understood. To address this, we performed joint microbiome and metabolome characterization of fecal samples over the course of experimental acute and chronic Chagas disease, using 16S rRNA sequencing and liquid chromatography-tandem mass spectrometry. These results showed functional changes in the fecal microbiome, beginning in the acute stage prior to peak parasite burden. Importantly, these changes persisted in the chronic stage of disease. Alterations include perturbations in conjugated linoleic acid (CLA) derivatives and in specific members of families *Ruminococcaceae* and *Lachnospiraceae*, as well as changes in secondary bile acid levels and members of order Clostridiales, all of which could have local as well as systemic effects on *T. cruzi* persistence and inflammation. In addition, we assessed microbial and metabolic changes systematically throughout the gastrointestinal tract. This enabled us to build a three-dimensional model of functional microbiome disturbances, in correlation with localized parasite burden. The greatest microbial disruptions were observed in the colon, where parasite burden was the highest, and in the esophagus, in association with changes in small molecule profile. Overall, these results are expanding our understanding of Chagasic megacolon and megaoesophagus pathogenesis, with great potential for the development of novel intervention strategies against this neglected tropical disease.

1404

MODELLING THE EFFECTS OF ATTRACTIVE TOXIC SUGAR BAITS (ATSBS) ON MALARIA PREVALENCE IN HUMANS; A TOOL FOR EPIDEMIOLOGICAL STUDY DESIGN

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Attractive toxic sugar baits (ATSBs) are a promising new tool for malaria control as they can potentially target outdoor-feeding mosquito populations, in contrast to the current vector control tools which predominantly focus on indoor-feeding mosquitoes. A Phase II efficacy trial with entomological endpoints is currently underway in Mali. To inform the design of subsequent Phase III epidemiological trials, we developed mathematical models to explore the potential impact on human endpoints of ATSBs in different transmission settings. A critical parameter determining efficacy is the sugar-feeding rate, which can vary between locations (due to availability of other food sources) and seasonally (due to variation in abundance of vegetation with rainfall). In a moderate-to-high-transmission setting such as Mali, with a 3-4 month peak transmission season and an annual average human prevalence in 2-10 year olds (PrP_{2-10}) of 50%, a sugar-feeding rate of 0.4/day (similar to that estimated from past field trials) is predicted to reduce the year-round average mosquito density in the second year of ATSB implementation by ~90% compared to the pre-intervention average. Because the increase in death rate caused by ATSBs induces a greater reduction in the population of older mosquitoes, we predict a higher reduction in EIR (>99.9%) and hence a ~92% reduction in PrP_{2-10}. Smaller but still significant effects on PrP_{2-10} are predicted with a lower sugar feeding rate (~90% for a rate of 0.2/day, ~68% for a rate of 0.1/day, ~36% for a rate of 0.05/day). Higher sugar feeding rates during the dry season and lower rates during the rainy season are predicted to modify the impact whilst movement of mosquitoes from untreated into treated areas is also expected to reduce the overall efficacy. Further outputs for a range of locations and additional human endpoints such as clinical incidence will be presented, allowing a full exploration of the potential impact of this new vector control tool across malaria-endemic settings.

1405

SIMULATION STUDIES TO QUANTIFY THE IMPACT OF COMPETING RISK EVENTS IN A HYPOTHETICAL SCENARIO OF FALLING ANTIMALARIAL DRUG EFFICACY IN SINGLE-ARMED AND COMPARATIVE DRUG TRIALS

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A new infection (NI) can potentially preclude the occurrence of a subsequent recrudescence, thus constituting a competing risk event (CRE). In the presence of CRE, the complement of the Kaplan Meier (K-M) estimate is known to result in an overestimate of failure. The overall aim of this simulation work was to quantify the bias in derived failure due to the use of the K-M method (which censors NI) compared to the Cumulative Incidence Function (CIF) approach (which considers NI as a CRE), and to assess the impact of CRE on comparative efficacy. A clinical trial (n=500 patients) was simulated with 5, 10 and 15% documented recrudescences. For each scenario, different proportions of NI were simulated to represent areas of progressively increasing transmission (<10%, 10-20%, 20-40% and >40%). Time to recrudescence and NI were simulated using biologically plausible hazard functions. For comparative studies, nine different scenarios which could be observed in a field trial when comparing two drugs (drug A and drug B) were simulated. For each of these scenarios, log-rank test for comparing the equality of K-M curves and Gray's test for comparing the equality of the CIFs were used. In single-armed trial, the overestimation of failure by the K-M method increased with increasing proportion of NI. In high transmission areas, the maximum overestimation in efficacy was 0.75% at 5% recrudescence and this rose to 3.1% and 4.3% when the drug efficacy fell to 90% and 85% respectively. In comparative trial, where drug B was associated with 2-fold increase in both recrudescence and NI (compared to drug A), the log-rank test appeared to be the more powerful test with a rejection probability of 99% compared to 90% with Gray's test. However, when drug B exerted differential effect on recrudescence and NI (i.e. reduced

recrudescence but increased NI), the Gray's test was the more powerful of the two tests. In high transmission areas, where the risk of new infection is high, the competing risk analysis approach should be used for deriving failure estimates. For comparative trials, the choice of the test to establish difference should be guided by the research question of interest.

1406

MULTIPLE FIRST LINE THERAPIES VERSUS REDUCING OVERPRESCRIPTION OF ANTIMALARIALS TO SLOW ANTIMALARIAL RESISTANCE

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The emergence of artemisinin and partner drug resistance prompts examination of which strategies can best delay or prevent the spread of resistance. It is unlikely that countries can implement all strategies simultaneously given resource constraints. Some countries are adopting a policy of multiple first-line therapies (MFT), where different patients are allocated to different ACTs, to increase the diversity of selective pressures acting on the parasite. However, there are barriers to implementing MFT, in particular the logistics of distribution as well as patient acceptance. Another measure, which many countries are also implementing, is to reduce overprescription of antimalarials, which can occur in the absence of diagnostic tests. We use model-based analysis to investigate whether reducing overprescription of antimalarials could be as effective as MFT in delaying drug resistance. We developed an individual based model of malaria transmission incorporating treatment with combination therapies, malaria parasites with different genotypes (wild type, resistant to each possible combination of antimalarials), heterogeneity in exposure to infectious bites, immunity to clinical manifestations of malaria, and fitness costs of resistance. We varied key parameters such as treatment coverage, the proportion of infections which develop symptoms, and the degree of resistance to each strain. We quantified the effectiveness of each strategy as the cumulative number of treatment failures over time. Initial results show that reducing overprescription of antimalarials is predicted to have more relative effect in delaying resistance in high transmission areas, where selection occurs during reinfection. The effect of reducing overprescription is small in low to moderate transmission areas. There is a non-linear relationship between treatment coverage with any one drug among clinical cases, and time to reach 10% resistance, such that if it were possible to use 5 or more different drugs for MFT, resistance development may be substantially delayed. Ongoing analysis will compare the benefits of the two strategies under different scenarios.

1407

PHARMACOKINETIC/PHARMACODYNAMIC MODELING TO OPTIMIZE DIHYDROARTEMISININ-PIPERAQUINE EXPOSURE AND PREVENT SELECTION FOR MARKERS OF DECREASED ANTIMALARIAL DRUG SENSITIVITY DURING INTERMITTENT PREVENTIVE TREATMENT DURING PREGNANCY

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Dihydroartemisinin-piperaquine (DP) is under study for intermittent preventive treatment during pregnancy (IPTp), but its use may accelerate selection for drug resistance. We aimed first, to define the relationship between piperaquine (PQ) exposure and genetic markers associated with decreased drug susceptibility, and second, to predict optimized DP dosing regimens to minimize risk of resistance. Clinical data, PQ concentrations, and *P. falciparum* genotypes associated with decreased PQ sensitivity in Africa (*pfmdr1* 86Y, *pfcrt* 76T) were obtained from pregnant Ugandan women who received IPTp with sulfadoxine-pyrimethamine (SP) every 8 weeks (n=106), DP every 4 weeks (n=100), or DP every 8 weeks (n=94). Joint pharmacokinetic/pharmacodynamic models were developed to describe the relationship between PQ concentration and the probability of detecting genotypes of interest using nonlinear mixed effects modeling; monthly, weekly, and daily DP regimens were simulated. Increasing PQ concentration was associated with a log-linear decrease in detection of parasitemia. Higher median PQ concentrations were needed to provide 99% protection against mutant infections as compared to wild type (N86: 7.2 ng/mL; 86Y: 10.8 ng/mL; K76: 4.9 ng/mL; 76T: 11.0 ng/mL). The median percentage of time at risk (PQ levels below those offering 99% protection) with monthly DP was 4.2% (interquartile range (IQR): 0-21%) for *pfmdr1* N86, 34% (IQR: 9.3-52%) for *pfmdr1* 86Y ($p<.01$), 0% (IQR: 0-2.6%) for *pfcrt* K76, and 31% (IQR: 10-54%) for *pfcrt* 76T ($p<.01$). Daily low dose DP was predicted to reduce the median percentage of time at risk for any parasitemia to <1% and to result in the fewest mutant infections (episodes of *pfmdr1* 86Y parasitemia per 1,000 pregnancies: SP: 332, monthly DP: 190, weekly DP: 52, daily DP: 0). Our models predict that 1) higher PQ concentrations are needed to prevent infections with mutant compared to wild type parasites, 2) the overall burden of infections with mutant parasites is lower for DP than SP, and 3) daily low dose DP best reduced the estimated number of mutant infections. Consideration of dose optimization of DP for IPTp in Africa is warranted.

1408

PHARMACOKINETIC-PHARMACODYNAMIC MODELLING OF ARTESUNATE IN PATIENTS WITH DRUG RESISTANT AND SENSITIVE MALARIA (TRAC)

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The emergence of artemisinin resistance in Southeast Asia is a substantial threat to currently used antimalarial therapies and it is important to optimize current treatments to maximize therapeutic efficacy. This project aimed to investigate the pharmacokinetic and pharmacodynamic properties of artesunate, and to quantify the impact of resistance on therapeutic outcome. Pharmacokinetic and pharmacodynamic data presented here were generated from the Tracking Resistance to Artemisinin Collaboration (TRAC). Hitherto, this is the largest study ever conducted, investigating the pharmacokinetic and pharmacodynamic properties of artesunate. A total of 1,180 patients in Asia and Africa with uncomplicated *falciparum* malaria, receiving daily monotherapy of artesunate for three days, contributed data to this analysis. Densely collected plasma concentrations of artesunate and dihydroartemisinin, microscopy parasite counts and molecular markers for drug resistance were collected and analysed using nonlinear mixed-effect modelling. Artesunate and dihydroartemisinin pharmacokinetics were well-described by a parent-metabolite model, assuming full *in-vivo* conversion of artesunate into dihydroartemisinin. Parasite density measurements were modelled using a fixed 10-fold multiplication growth rate per parasite life-cycle. The elimination of parasites was dependent on the concentration of dihydroartemisinin and was described by an E_{MAX} model. Mutation of the K13-propeller, associated with reduced drug susceptibility, had a significant impact on the maximum effect, resulting in a slower killing of parasites in patients with drug resistant infections. The developed model was used to simulate different treatment alternatives for patients with artemisinin resistant infections, demonstrating that an increased treatment duration of current combination therapy is necessary in these patients. Alternatively, triple combination of antimalarial drugs are under evaluation to treat resistant infections.