Réseau MTN Francophone

Veille scientifique
Maladies tropicales négligées

Semaine 12

21 mars 2022 – 28 mars 2022

DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Double Negative Control Inference in Test-Negative Design Studies of Vaccine Effectiveness.

Li, K., Shi, X., Miao, W., Tchetgen, E.
23-03-2022
ArXiv
https://pubmed.ncbi.nlm.nih.gov/35350548

The test-negative design (TND) has become a standard approach to evaluate vaccine effectiveness against the risk of acquiring infectious diseases in real-world settings, such as Influenza, Rotavirus, Dengue fever, and more recently COVID-19. In a TND study, individuals who experience symptoms and seek care are recruited and tested for the infectious disease which defines cases and controls. Despite TND's potential to reduce unobserved differences in healthcare seeking behavior (HSB) between vaccinated and unvaccinated subjects, it remains subject to various potential biases. First, residual confounding bias may remain due to unobserved HSB, occupation as healthcare worker, or previous infection history. Second, because selection into the TND sample is a common consequence of infection and HSB, collider stratification bias may exist when conditioning the analysis on testing, which further induces confounding by latent HSB. In this paper, we present a novel approach to identify and estimate vaccine effectiveness in the target population by carefully leveraging a pair of negative control exposure and outcome variables to account for potential hidden bias in TND studies. We illustrate our proposed method with extensive simulation and an application to study COVID-19 vaccine effectiveness using data from the University of Michigan Health System.

CHIKV strains Brazil (wt) and Ross (lab-adapted) differ with regard to cell host range and antiviral sensitivity and show CPE in human glioblastoma cell lines U138 and U251.

Hucke, F., Bestehorn-Willmann, M., Bassetto, M., Brancale, A., Zanetta, P., Bugert, J.
26-03-2022
Virus Genes
https://doi.org/10.1007/s11262-022-01892-x

Chikungunya virus (CHIKV), a (re)emerging arbovirus, is the causative agent of chikungunya fever. To date, no approved vaccine or specific antiviral therapy are available. CHIKV has repeatedly been responsible for serious economic and public health impacts in countries where CHIKV epidemics occurred. Antiviral tests in vitro are generally performed in Vero-B4 cells, a well characterised cell line derived from the kidney of an African green monkey. In this work we characterised a CHIKV patient isolate from Brazil ($CHIKV^{Brazil}$) with regard to cell affinity, infectivity, propagation and cell damage and compared it with a high-passage lab strain ($CHIKV^{Ross}$). Infecting various cell lines (Vero-B4, A549, Huh-7, DBTRG, U251, and U138) with both virus strains, we found distinct differences between the two viruses. $CHIKV^{Brazil}$ does not cause cytopathic effects (CPE) in the human hepatocarcinoma cell line Huh-7. Neither $CHIKV^{Brazil}$ nor $CHIKV^{Ross}$ caused CPE on A549 human lung epithelial cells. The human astrocyte derived glioblastoma cell lines U138 and U251 were found to be effective models for lytic infection with both virus strains and we discuss their predictive potential for neurogenic CHIKV disease. We also detected significant differences in antiviral efficacies regarding the two CHIKV strains. Generally, the antivirals ribavirin, hydroxychloroquine (HCQ) and T-1105 seem to work better against $CHIKV^{Brazil}$ in glioblastoma cells than in Vero-B4. Finally, full genome analyses of the CHIKV isolates were done in order to determine their lineage and possibly explain differences in tissue range and antiviral compound efficacies.

ATP-sensitive inward rectifier potassium channels reveal functional linkage between salivary gland function and blood feeding in the mosquito, Aedes aegypti.

Li, Z., Soohoo-Hui, A., O'Hara, F., Swale, D.
28-03-2022
Commun Biol
https://doi.org/10.1038/s42003-022-03222-1

Reducing saliva secretions into the vertebrate host reduces feeding efficacy by most hematophagous arthropods. However, seminal studies suggested saliva is not a prerequisite for blood feeding in Aedes aegypti. To test this paradigm, we manually transected the salivary duct of female A. aegypti and an inability to salivate was correlated to an inability to imbibe blood. These data justified testing the relevance of inwardly rectifying potassium (Kir) channels in the A. aegypti salivary gland as an antifeedant target site. Pharmacological activation of ATP-gated Kir (K_{ATP}) channels reduced the secretory activity of the salivary gland by 15-fold that led to near elimination of blood ingestion during feeding. The reduced salivation and feeding success nearly eliminated horizontal transmission and acquisition of Dengue virus-2 (DENV2). These data suggest mosquito salivation is a prerequisite for blood feeding and provide evidence that K_{ATP} channels are critical for salivation, feeding, and vector competency.

An Epidemic Zika Virus Isolate Drives Enhanced T Follicular Helper Cell and B Cell-Mediated Immunity.

Pardy, R., Gentile, M., Carter, A., Condotta, S., King, I., Richer, M.
28-03-2022
J Immunol
https://pubmed.ncbi.nlm.nih.gov/35346966

Zika virus (ZIKV) is a mosquito-borne pathogen that recently caused a series of increasingly severe outbreaks. We previously demonstrated that, compared with a pre-epidemic isolate ($ZIKV^{CDN}$), a Brazilian ZIKV isolate ($ZIKV^{BR}$) possesses a

novel capacity to suppress host immunity, resulting in delayed viral clearance. However, whether ZIKV^{BR} modulates CD4 T cell responses remains unknown. In this study, we show that, in comparison with ZIKV^{CDN} infection, CD4 T cells are less polarized to the Th1 subtype following ZIKV^{BR} challenge in mice. In contrast, we observed an enhanced accumulation of T follicular helper cells 10, 14, and 21 d postinfection with ZIKV^{BR} This response correlated with an enhanced germinal center B cell response and robust production of higher avidity-neutralizing Abs following ZIKV^{BR} infection. Taken together, our data suggest that contemporary ZIKV strains have evolved to differentially induce CD4 T cell, B cell, and Ab responses and this could provide a model to further define the signals required for T follicular helper cell development.

Mouse circulating extracellular vesicles contain virus-derived siRNAs active in antiviral immunity.

Zhang, Y., Dai, Y., Wang, J., Xu, Y., Li, Z., Lu, J., Xu, Y., Zhong, J., Ding, S., Li, Y.
28-03-2022
EMBO J
https://doi.org/10.15252/embj.2021109902

Induction and suppression of antiviral RNA interference (RNAi) has been observed in mammals during infection with at least seven distinct RNA viruses, including some that are pathogenic in humans. However, while the cell-autonomous immune response mediated by antiviral RNAi is gradually being recognized, little is known about systemic antiviral RNAi in mammals. Furthermore, extracellular vesicles (EVs) also function in viral signal spreading and host immunity. Here, we show that upon antiviral RNAi activation, virus-derived small-interfering RNAs (vsiRNAs) from Nodamura virus (NoV), Sindbis virus (SINV), and Zika virus (ZIKV) enter the murine bloodstream via EVs for systemic circulation. vsiRNAs in the EVs are biologically active, since they confer RNA-RNA homology-dependent antiviral activity in both cultured cells and infant mice. Moreover, we demonstrate that vaccination with a live-attenuated virus, rendered deficient in RNAi suppression, induces production of stably maintained vsiRNAs and confers protective immunity against virus infection in mice. This suggests that vaccination with live-attenuated VSR (viral suppressor of RNAi)-deficient mutant viruses could be a new strategy to induce immunity.

Chikungunya virus time course infection of human macrophages reveals intracellular signaling pathways relevant to repurposed therapeutics.

Gray, M., Guerrero-Arguero, I., Solis-Leal, A., Robison, R., Berges, B., Pickett, B.
21-03-2022
PeerJ
https://doi.org/10.7717/peerj.13090

Chikungunya virus (CHIKV) is a mosquito-borne pathogen, within the *Alphavirus* genus of the *Togaviridae* family, that causes ~1.1 million human infections annually. CHIKV uses *Aedes albopictus* and *Aedes aegypti* mosquitoes as insect vectors. Human infections can develop arthralgia and myalgia, which results in debilitating pain for weeks, months, and even years after acute infection. No therapeutic treatments or vaccines currently exist for many alphaviruses, including CHIKV. Targeting the phagocytosis of CHIKV by macrophages after mosquito transmission plays an important role in early productive viral infection in humans, and could reduce viral replication and/or symptoms. To better characterize the transcriptional response of macrophages during early infection, we generated RNA-sequencing data from a CHIKV-infected human macrophage cell line at eight or 24 hours post-infection (hpi), together with mock-infected controls. We then calculated differential gene expression, enriched functional annotations, modulated intracellular signaling pathways, and predicted therapeutic drugs from these sequencing data. We observed 234 pathways were significantly affected 24 hpi, resulting in six potential pharmaceutical treatments to modulate the affected pathways. A subset of significant pathways at 24 hpi includes AGE-RAGE, Fc epsilon RI, Chronic myeloid leukemia, Fc gamma R-mediated phagocytosis, and Ras signaling. We found that the MAPK1 and MAPK3 proteins are shared among this subset of pathways and that Telmisartan and Dasatinib are strong candidates for repurposed small molecule therapeutics that target human processes. The results of our analysis can be further characterized in the wet lab to contribute to the development of host-based prophylactics and therapeutics.

Therapeutic and prophylactic treatment with a virus-specific antibody is highly effective in rodent models of Chikungunya infection and disease.

Julander, J., Anderson, N., Haese, N., Andoh, T., Streblow, D., Cortez, P., Carter, K., Marniquet, X., Watson, H., Mandron, M.
23-03-2022
Antiviral Res
https://pubmed.ncbi.nlm.nih.gov/35339583

Chikungunya virus (CHIKV) has re-emerged as a significant human pathogen in the 21st century, causing periodic, and sometimes widespread, outbreaks over the past 15 years. Although mortality is very rare, a debilitating arthralgia is very common and may persist for months or years. There are no antivirals that are approved for the treatment of CHIKV infection, and current treatment options consist of supportive care only. Herein, we demonstrate the efficacy of a CHIKV-specific antibody in the prophylactic and therapeutic treatment of CHIKV in mouse models of disease. The fully human anti-CHIKV monoclonal Ab SVIR023 demonstrated broad in vitro activity against representative strains from the three major CHIKV clades. Therapeutic treatment with SVIR023 administered 1- or 3-days post-infection resulted in reduced virus in various tissues in a dose- and time-dependent manner. Prophylactic treatment up to 4 weeks prior to virus challenge was also effective in preventing disease in mice. Mice treated with SVIR023 and infected with CHIKV were resistant to secondary challenge and no evidence of antibody enhancement of disease was observed. Treatment with

SVIR023 was effective in mouse models of CHIKV infection and disease and further evaluation towards clinical development is warranted.

Pneumonia, influenza, and dengue cases decreased after the COVID-19 pandemic in Thailand.

Prasertbun, R., Mori, H., Mahittikorn, A., Siri, S., Naito, T.
25-03-2022
Trop Med Health
https://doi.org/10.1186/s41182-022-00419-2

The coronavirus disease 2019 (COVID-19) pandemic has affected all healthcare systems worldwide. Effective COVID-19 preventive measures, including wearing a mask, hand washing, avoiding the "Three Cs", and city lockdowns, could decrease other infectious diseases. The case numbers of the major infectious diseases in Thailand were investigated (pneumonia, influenza, and dengue fever) during the COVID-19 pandemic using Thailand government national data sources from 2018 to August 2021. Pneumonia, influenza, and dengue fever cases decreased after the COVID-19 pandemic. In addition to respiratory tract infections, COVID-19 preventive measures could decrease dengue fever cases.

Phenotypic and Kinetic Changes of Myeloid Lineage Cells in Innate Response to Chikungunya Infection in Cynomolgus Macaques.

Beddingfield, B., Sugimoto, C., Wang, E., Weaver, S., Russell-Lodrigue, K., Killeen, S., Kuroda, M., Roy, C.
25-03-2022
Viral Immunol
https://doi.org/10.1089/vim.2021.0171

Chikungunya (CHIKV) is an emerging worldwide viral threat. The immune response to infection can lead to protection and convalescence or result in long-term sequelae such as arthritis. Early innate immune events during acute infection have been characterized for some cell types, but more must be elucidated with respect to cellular responses of monocytes and other myeloid lineage cells. In addition to their roles in protection and inflammation resolution, monocytes and macrophages are sites for viral replication and may also act as viral reservoirs. These cells are also found in joints postinfection, possibly playing a role in long-term CHIKV-induced pathology. We examined kinetic and phenotypic changes in myeloid lineage cells, including monocytes, in cynomolgus macaques early after experimental infection with CHIKV. We found increased proliferation of monocytes and decreased proliferation of myeloid dendritic cells early during infection, with an accompanying decrease in absolute numbers of both cell types, as well as a simultaneous increase in plasmacytoid dendritic cell number. An increase in CD16 and CD14 was seen along with a decrease in monocyte Human Leukocyte Antigen-DR isotype expression within 3 days of infection, potentially indicating monocyte deactivation. A transient decrease in T cells, B cells, and natural killer cells correlated with lymphocytopenia observed during human infections with CHIKV. $CD4^+$ T cell proliferation decreased in blood, indicating relocation of cells to effector sites. These data indicate CHIKV influences proliferation rates and kinetics of myeloid lineage cells early during infection and may prove useful in development of therapeutics and evaluation of infection-induced pathogenesis.

Stem cell-based region-specific brain organoids: Novel models to understand neurodevelopmental defects.

Revue de littérature

Shafique, S.
25-03-2022
Birth Defects Res
https://doi.org/10.1002/bdr2.2004

The study of human brain development and neurodevelopmental defects has remained challenging so far due to unique, specific, and complex underlying processes. Recent advances in the technologies and protocols of in vitro human brain organoid development have led to immense possibilities of understanding these processes. Human brain organoids are stem-cell derived three-dimensional in vitro tissues that resemble the developing fetal brain. Major advances in stem cell techniques pioneering the development of in vitro human brain development include reprogramming human somatic cells into induced pluripotent cells (iPSCs) followed by the targeted differentiation of iPSCs into the cells of three embryonic germ cell layers. The neural progenitor cells produced by the directed differentiation of iPSCs undergo some level of self-organization to generate in vitro human brain like tissue. A three-dimensional differentiation approach applied to create region-specific brain organoids has successfully led to develop highly specialized cortical, forebrain, pallium, and subpallium in vitro human brain organoid models. These stem cell-based brain organoids are novel models to study human brain development, neurodevelopmental defects, chemical toxicity testing, and drug repurposing screening. This review focuses on the fundamentals of brain organoid development and applications. The novel applications of using cortical organoids in understanding the mechanisms of Zika virus-induced microcephaly, congenital microcephaly, and lissencephaly are also discussed.

Identifying possible inaccuracy in reported birth head circumference measurements among infants in the US Zika Pregnancy and Infant Registry.

Roth, N., Woodworth, K., Godfred-Cato, S., Delaney, A., Olson, S., Nahabedian, J., Reynolds, M., Jones, A., Neelam, V., Valencia-Prado, M., Delgado-López, C., Lee, E., Ellis, E., Lake-Burger, H., Tonzel, J., Higgins, C., Chan, R., Tong, V., Gilboa, S., Cragan, J., Honein, M., Moore, C.
25-03-2022
Birth Defects Res
https://doi.org/10.1002/bdr2.1997

The US Zika Pregnancy and Infant Registry (USZPIR) monitors infants born to mothers with confirmed or possible Zika virus infection during pregnancy. The surveillance case definition for Zika-associated birth defects includes microcephaly based on head circumference (HC). We assessed birth and follow-up data from infants with birth HC measurements <3rd percentile and birthweight ≥10th percentile to determine possible misclassification of microcephaly. We developed a schema informed by literature review and expert opinion to identify possible HC measurement inaccuracy using HC growth velocity and longitudinal HC measurements between 2 and 12 months of age. Two or more HC measurements were required for assessment. Inaccuracy in birth HC measurement was suspected if growth velocity was >3 cm/month in the first 3 months or HC was consistently >25th percentile during follow-up. Of 6,799 liveborn infants in USZPIR, 351 (5.2%) had Zika-associated birth defects, of which 111 had birth HC measurements <3rd percentile and birthweight ≥10th percentile. Of 84/111 infants with sufficient follow-up, 38/84 (45%) were classified as having possible inaccuracy of birth HC measurement, 19/84 (23%) had HC ≥3rd percentile on follow-up without meeting criteria for possible inaccuracy, and 27/84 (32%) had continued HC <3rd percentile. After excluding possible inaccuracies, the proportion of infants with Zika-associated birth defects including microcephaly decreased from 5.2% to 4.6%. About one-third of infants in USZPIR with Zika-associated birth defects had only microcephaly, but indications of possible measurement inaccuracy were common. Implementation of this schema in longitudinal studies can reduce misclassification of microcephaly.

Global mapping of RNA homodimers in living cells.

Gabryelska, M., Badrock, A., Lau, J., O'Keefe, R., Crow, Y., Kudla, G.
24-03-2022
Genome Res
https://pubmed.ncbi.nlm.nih.gov/35332098

RNA homodimerization is important for various physiological processes, including the assembly of membraneless organelles, RNA subcellular localization, and packaging of viral genomes. However, understanding of RNA dimerization has been hampered by the lack of systematic in vivo detection methods. Here we show that CLASH, PARIS, and other RNA proximity ligation methods detect RNA homodimers transcriptome-wide as "overlapping" chimeric reads that contain more than one copy of the same sequence. Analyzing published proximity ligation datasets, we show that RNA:RNA homodimers mediated by direct base-pairing are rare across the human transcriptome, but highly enriched in specific transcripts, including *U8* snoRNA, *U2* snRNA and a subset of tRNAs. Mutations in the homodimerization domain of *U8* snoRNA impede dimerization in vitro and disrupt zebrafish development in vivo, suggesting an evolutionarily conserved role of this domain. Analysis of virus-infected cells reveals homodimerization of SARS-CoV-2 and Zika genomes, mediated by specific palindromic sequences located within protein-coding regions of *N* gene in SARS-CoV-2 and *NS2A* gene in Zika. We speculate that regions of viral genomes involved in homodimerization may constitute effective targets for antiviral therapies.

Megacity-centric mass mobility during Eid holidays: a unique concern for infectious disease transmission in Bangladesh.

Hossain, M.
24-03-2022
Trop Med Health
https://doi.org/10.1186/s41182-022-00417-4

Human mobility, particularly during certain festivals in rapidly growing megacities in low- and middle-income countries, has critical implications in infectious diseases surveillance and preparedness. In this perspective, we present the interesting case of Dhaka megacity, the capital of Bangladesh with a population of over 20 million. In recent times, three massive infectious disease outbreaks in Dhaka (chikungunya, dengue and COVID-19) coincided with Muslim religious Eid festivals. From a public health standpoint, it is very important to share this information with the international community to fight against emerging infectious diseases around the world.

Saliva collection via capillary method may underestimate arboviral transmission by mosquitoes.

Gloria-Soria, A., Brackney, D., Armstrong, P.
24-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05198-7

Arthropod-borne viruses (arboviruses) impose a major health and economic burden on human populations globally, with mosquitoes serving as important vectors. Measuring the ability of a mosquito population to transmit an arbovirus is important in terms of evaluating its public health risk. In the laboratory, a variety of methods are used to estimate arboviral transmission by mosquitoes, including indirect methods involving viral detection from mosquito saliva collected by forced salivation. The accuracy of indirect methods to estimate arbovirus transmission to live animal hosts has not been fully evaluated. We compared three commonly used proxies of arboviral transmission, namely, the presence of virus in mosquito legs, in salivary glands (SG) and in saliva collected in capillary tubes using forced salivation, with direct transmission estimates from mosquitoes to suckling mice. We analyzed five vector-virus combinations, including Aedes aegypti infected with chikungunya virus, West Nile virus and Zika virus; Culex quinquefasciatus infected with West Nile virus; and Aedes triseriatus infected with La Crosse virus. Comparatively, the methods of detecting virus infection in mosquito legs and in SG were equally accurate in predicting transmission. Overall, the presence of virus in mosquito legs was a more accurate predictor of transmission than the commonly implemented viral detection method using forced

salivation into a capillary tube, and was subject to less technical variation. These results suggest that, in general, forced salivation methods tend to underestimate virus transmission, and they provide confidence in the use of mosquito leg screens to evaluate the transmission potential of a mosquito population.

The association of ultrasound assessment of gallbladder wall thickness with dengue fever severity.

Ibrahim, M., Hamzah, S., Md Noor, J., Mohamad, M., Mokhtar, M., Isa, M., Abdul Rani, M.
24-03-2022
Ultrasound J
https://doi.org/10.1186/s13089-022-00262-w

To evaluate the association between ultrasound assessment of gallbladder wall thickness (GBWT) among severe dengue patients and dengue patients with warning signs to their clinical outcomes. A prospective, cross-sectional study involving adult dengue patients presented to our emergency department between March until September 2018. The patients were classified based on WHO classification. A gallbladder wall scan was performed on all patients. A total of 44 patients were enrolled into the study; majority of the patients with GBWT had severe dengue, significantly more than the dengue patients with warning signs (90.5% sensitivity; 69.6% specificity). The sensitivity of GBWT in determining admission to critical care areas or general ward was 100% with a specificity of 62.1%. Our analysis showed that the two variables significant in determining the severity of dengue were age ($p=0.045$) and GBWT ($p<0.001$). Both factors together gave 81.0% sensitivity and 78.3% specificity in predicting patients for severe dengue. The receiver operator characteristic curve revealed that using variable GBWT status can discriminate 87.1% (95%CI 66.3, 93.7%) of having severe dengue or dengue with warning signs. The finding of GBWT when consolidated with other clinical parameters may assist clinicians to perform risk stratification in the emergency department and become another adjunct to the assessment of severe dengue.

Bilateral Ciliochoroidal Effusion with Secondary Angle Closure and Myopic Shift in Dengue Fever.

Dhoot, S.
24-03-2022
Ocul Immunol Inflamm
https://doi.org/10.1080/09273948.2022.2053548

To describe a case of bilateral ciliochoroidal effusion with secondary angle closure and myopic shift early in course of Dengue Fever. A 36-year-old, female complaints of painless loss of vision few days after being diagnosed dengue fever. Her best corrected visual acuity is 6/6 with refractive correction of -3.00 DS and -2.75 DS in right and left eye respectively. On examination her anterior chambers are shallow with closed angles on anterior segment optical coherence tomography and high intraocular pressure. Fundus examination revealed macular striae with peripheral choroidal oedema suggestive of ciliochoroidal effusion with angle closure and acute myopic shift. Few days after starting on topical intraocular pressure lowering drugs, cycloplegics and topical steroid eye drops along with low dose systemic steroids her condition improved with resolution of choroidal effusion and return of vision to normal levels. This case report represents interesting patient who developed transient loss of vision due to accumulation of fluid in suprachoroidal space resulting in secondary angle closure and myopia after being diagnosed with dengue fever, for which one should have high index of suspicion to facilitate timely management.

A wMel Wolbachia variant in Aedes aegypti from field-collected Drosophila melanogaster with increased phenotypic stability under heat stress.

Gu, X., Ross, P., Rodriguez-Andres, J., Robinson, K., Yang, Q., Lau, M., Hoffmann, A.
23-03-2022
Environ Microbiol
https://doi.org/10.1111/1462-2920.15966

Mosquito-borne diseases remain a major cause of morbidity and mortality. Population replacement strategies involving the wMel strain of Wolbachia are being used widely to control mosquito-borne diseases. However, these strategies may be influenced by temperature because wMel is vulnerable to heat. wMel infections in Drosophila melanogaster are genetically diverse, but few transinfections of wMel variants have been generated in Aedes aegypti. Here, we successfully transferred a wMel variant (termed wMelM) originating from a field-collected D. melanogaster into Ae. aegypti. The new wMelM variant (clade I) is genetically distinct from the original wMel transinfection (clade III), and there are no genomic differences between wMelM in its original and transinfected host. We compared wMelM with wMel in its effects on host fitness, temperature tolerance, Wolbachia density, vector competence, cytoplasmic incompatibility and maternal transmission under heat stress in a controlled background. wMelM showed a higher heat tolerance than wMel, likely due to higher overall densities within the mosquito. Both wMel variants had minimal host fitness costs, complete cytoplasmic incompatibility and maternal transmission, and dengue virus blocking under laboratory conditions. Our results highlight phenotypic differences between Wolbachia variants and wMelM shows potential as an alternative strain in areas with strong seasonal temperature fluctuations.

Design of a multi-epitope Zika virus vaccine candidate - an *in-silico* study.

Ezzemani, W., Windisch, M., Altawalah, H., Guessous, F., Saile, R., Benjelloun, S., Kettani, A., Ezzikouri, S.
23-03-2022
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2022.2055648

Zika virus (ZIKV), an RNA virus, rapidly spreads *Aedes* mosquito-borne sickness. Currently, there are neither effective vaccines nor therapeutics available to prevent or treat ZIKV infection. In this study, to address these unmet medical needs, we aimed to design B- and T-cell candidate multi-epitope-based subunit against ZIKV using an *in silico* approach. In this study we applied immunoinformatics, molecular docking, and dynamic simulation assessments targeting the most immunogenic proteins; the capsid (C), envelope (E) proteins and the non-stuctural protein (NS1), described in our previous study, and which predicted immunodominant B and T cell epitopes. The final non-allergenic and highly antigenic multi-epitope was constituted of immunogenic screened-epitopes (3 CTL and 3 HTL) and the β-defensin as an adjuvant that have been linked using EAAAK, AAY, and GPGPG linkers, respectively. The final construct containing 143 amino acids was characterized for its allergenicity, antigenicity, and physiochemical properties; and found to be safe and immunogenic with a good prediction of solubility. The existence of IFN-γ epitopes asserts the capacity to trigger strong immune responses. Subsequently, the molecular docking among vaccine and immune receptors (TLR2/TLR4) was revealed with a good binding affinity with and stable molecular interactions. Molecular dynamics simulation confirmed the stability of the complexes. Finally, the construct was subjected to *in silico* cloning demonstrating the efficiently of its expression in *E.coli.* However, this study needs the experimental validation to demonstrate vaccine safety and efficacy.Communicated by Ramaswamy H. Sarma.

Virological Surveillance of Aedes aegypti Vectors Identifies All Four Dengue Serotypes in a Hyperendemic Region.

Andrade, E., Figueiredo, L., Vilela, A., Rosa, J., Zibaoui, H., Kroon, E.
22-03-2022
Ecohealth
https://doi.org/10.1007/s10393-022-01583-x

Dengue virus (DENV) 1-4 is the etiological agent of dengue, the most important viral infection transmitted by Aedes spp mosquitoes to humans. Our goal was to identify the circulating DENV in Aedes aegypti collected in an area of Brazil where all four DENV serotypes had already been detected in humans, understand the epidemiology better, and to test the vector as a virological surveillance tool. Twenty-eight larvae pools and 174 females of Aedes aegypti were screened by reverse transcriptase quantitative polymerase chain reaction and semi-nested PCR assays. PCR products were sequenced, and phylogenetic analyses were performed. Nine larvae pools (32.1%) were positive for DENV, four (44.4%) with DENV-3, and five (55.6%) with more than one serotype. Fifteen females (8.6%) were positive for any DENV serotype. DENV-1 isolates belong to genotype V, DENV-2 to American-Asian genotype, DENV-3 to genotypes I and III, and DENV-4 to genotypes I and II. We demonstrate for the first time the co-circulation of all four DENV serotypes in larvae pools and adult Aedes aegypti in a hyperendemic area. This scenario represents a challenge for disease control and reinforces the importance of virological surveillance in the vector as a tool for predicting circulating DENV serotypes in humans.

Aquatain® causes anti-oviposition, egg retention and oocyte melanization and triggers female death in Aedes aegypti.

Dieng, H., McLean, S., Stradling, H., Morgan, C., Gordon, M., Ebanks, W., Ebanks, Z., Wheeler, A.
22-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05202-0

In arboviral disease systems where the virus can be transmitted from male to female vectors and from one generation to the next, targeting the female (especially when she is gravid) can help alter the persistence of the virus in nature and its transmission. A typical example is Aedes aegypti, which has become unmanageable due to the development of insecticide resistance. Despite evidence that monomolecular surface films prevent the selection of genetic resistance, their potential in Aedes vector control remains largely unexplored. We examined the oviposition, egg retention, oocyte melanization, and female mortality of the Cayman Islands strain of Ae. aegypti, using choice (balanced and unbalanced) and no-choice bioassays involving Aquatain® Mosquito Formulation (AMF; Aquatain Products Pty Ltd.), a polydimethylsiloxane-based liquid used for mosquito control. When presented with similar opportunities to oviposit in two sites treated with AMF and two other sites with untreated water (control), egg deposition rates were significantly higher in the untreated water sites than in the AMF-treated sites ($P<0.05$). We also observed a matching pattern of egg deposition preference in environments with more options in terms of AMF-treated sites. Females laid significantly more eggs when water was the only available medium than when all sites were treated with AMF ($P<0.05$). Also, significantly more mature eggs were withheld in the AMF no-choice environment than in the no-choice test involving only water ($P<0.05$). Internal oocyte melanization was not observed in females from the oviposition arenas with the lowest AMF presence (equal-choice and water-based no-choice); in contrast, this physiological response intensified as the number of AMF-treated sites increased. Female death occurred at high rates in AMF-treated environments, and this response increased with the increasing presence of such egg deposition sites. This study demonstrated that AMF acted as a deterrent signal to ovipositing Ae. aegypti and as an indirect adulticide. These results suggest that AMF may be a promising control tool against the dengue vector, and this warrants further evaluation under field settings.

MicroRNA 573 Rescues Endothelial Dysfunction during Dengue Virus Infection under PPARγ Regulation.

Banerjee, S., Xin, C., Chu, J.

23-03-2022
J Virol
https://doi.org/10.1128/jvi.01996-21

Early prognosis of abnormal vasculopathy is essential for effective clinical management of patients with severe dengue. An exaggerated interferon (IFN) response and release of vasoactive factors from endothelial cells cause vasculopathy. This study shows that dengue virus 2 (DENV2) infection of human umbilical vein endothelial cells (HUVEC) results in differentially regulated microRNAs (miRNAs) important for endothelial function. miR-573 was significantly downregulated in DENV2-infected HUVEC due to decreased peroxisome proliferator activator receptor gamma (PPARγ) activity. Restoring miR-573 expression decreased endothelial permeability by suppressing the expression of vasoactive angiopoietin 2 (ANGPT2). We also found that miR-573 suppressed the proinflammatory IFN response through direct downregulation of Toll-like receptor 2 (TLR2) expression. Our study provides a novel insight into miR-573-mediated regulation of endothelial function during DENV2 infection, which can be further translated into a potential therapeutic and prognostic agent for severe dengue patients. IMPORTANCE We need to identify molecular factors that can predict the onset of endothelial dysfunction in dengue patients. Increase in endothelial permeability during severe dengue infections is poorly understood. In this study, we focus on factors that regulate endothelial function and are dysregulated during DENV2 infection. We show that miR-573 rescues endothelial permeability and is downregulated during DENV2 infection in endothelial cells. This finding can have both diagnostic and therapeutic applications.

High-Titer Self-Propagating Capsidless Chikungunya Virus Generated in Vero Cells as a Strategy for Alphavirus Vaccine Development.

Zhang, Y., Zhang, Z., Li, N., Pei, X., Li, X., Deng, C., Ye, H., Zhang, B.
02-02-2022
J Virol
https://doi.org/10.1128/JVI.01480-21

In our previous study, we found that a new type of Chikungunya virus particle with a complete capsid deletion (ΔC-CHIKV) is still infectious in BHK-21 cells and demonstrated its potential as a live attenuated vaccine candidate. However, the low yield as well as the disability to propagate in vaccine production cell line Vero of ΔC-CHIKV are not practical for commercial vaccine development. In this study, we not only achieved the successful propagation of the viral particle in Vero cells, but significantly improved its yield through construction of a chimeric VEEV-ΔC-CHIKV and extensive passage in Vero cells. Mechanistically, high production of VEEV-ΔC-CHIKV is due to the improvement of viral RNA packaging efficiency conferred by adaptive mutations, especially those in envelope proteins. Similar to ΔC-CHIKV, the passaged VEEV-ΔC-CHIKV is safe, immunogenic, and efficacious, which protects mice from CHIKV challenge after only one shot of immunization. Our study demonstrates that the utilization of infectious capsidless viral particle of CHIKV as a vaccine candidate is a practical strategy for the development of alphavirus vaccine. IMPORTANCE Chikungunya virus (CHIKV) is one of important emerging alphaviruses. Currently, there are no licensed vaccines against CHIKV infection. We have previously found a new type of Chikungunya virus particle with a complete capsid deletion (ΔC-CHIKV) as a live attenuated vaccine candidate that is not suitable for commercial vaccine development with the low viral titer production. In this study, we significantly improved its production through construction of a chimeric VEEV-ΔC-CHIKV. Our results proved the utilization of infectious capsidless viral particle of CHIKV as a safe and practical vaccine candidate.

Perturbation of Alphavirus and Flavivirus Infectivity by Components of the Bacterial Cell Wall.

Langendries, L., Jacobs, S., Abdelnabi, R., Verwimp, S., Kaptein, S., Baatsen, P., Van Mellaert, L., Delang, L.
02-02-2022
J Virol
https://doi.org/10.1128/jvi.00060-22

The impact of the host microbiota on arbovirus infections is currently not well understood. Arboviruses are viruses transmitted through the bites of infected arthropods, predominantly mosquitoes or ticks. The first site of arbovirus inoculation is the biting site in the host skin, which is colonized by a complex microbial community that could possibly influence arbovirus infection. We demonstrated that preincubation of arboviruses with certain components of the bacterial cell wall, including lipopolysaccharides (LPS) of some Gram-negative bacteria and lipoteichoic acids or peptidoglycan of certain Gram-positive bacteria, significantly reduced arbovirus infectivity *in vitro*. This inhibitory effect was observed for arboviruses of different virus families, including chikungunya virus of the *Alphavirus* genus and Zika virus of the *Flavivirus* genus, showing that this is a broad phenomenon. A modest inhibitory effect was observed following incubation with a panel of heat-inactivated bacteria, including bacteria residing on the skin. No viral inhibition was observed after preincubation of cells with LPS. Furthermore, a virucidal effect of LPS on viral particles was noticed by electron microscopy. Therefore, the main inhibitory mechanism seems to be due to a direct effect on the virus particles. Together, these results suggest that bacteria are able to decrease the infectivity of alphaviruses and flaviviruses. IMPORTANCE During the past decades, the world has experienced a vast increase in epidemics of alphavirus and flavivirus infections. These viruses can cause severe diseases, such as hemorrhagic fever, encephalitis, and arthritis. Several alpha- and flaviviruses, such as chikungunya virus, Zika virus, and dengue virus, are significant global health threats because of their high disease burden, their widespread (re-)emergence, and the lack of (good) anti-arboviral strategies. Despite the clear health burden, alphavirus and flavivirus infection and disease are not fully understood. A knowledge gap in the interplay between the host and the arbovirus is the potential interaction with

host skin bacteria. Therefore, we studied the effect of (skin) bacteria and bacterial cell wall components on alphavirus and flavivirus infectivity in cell culture. Our results show that certain bacterial cell wall components markedly reduced viral infectivity by interacting directly with the virus particle.

Causes of fever in returning travelers: a European multicenter prospective cohort study.

Camprubí-Ferrer, D., Cobuccio, L., Van Den Broucke, S., Genton, B., Bottieau, E., d'Acremont, V., Rodriguez-Valero, N., Almuedo-Riera, A., Balerdi-Sarasola, L., Subirà, C., Fernandez-Pardos, M., Martinez, M., Navero-Castillejos, J., Vera, I., Llenas-Garcia, J., Rothe, C., Cadar, D., Van Esbroeck, M., Foque, N., Muñoz, J.
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J Travel Med
https://pubmed.ncbi.nlm.nih.gov/35040473

Etiological diagnosis of febrile illnesses in returning travelers is a great challenge, particularly when presenting with no focal symptoms [acute undifferentiated febrile illnesses (AUFI)], but is crucial to guide clinical decisions and public health policies. In this study, we describe the frequencies and predictors of the main causes of fever in travelers. Prospective European multicenter cohort study of febrile international travelers (November 2017-November 2019). A predefined diagnostic algorithm was used ensuring a systematic evaluation of all participants. After ruling out malaria, PCRs and serologies for dengue, chikungunya and Zika viruses were performed in all patients presenting with AUFI ≤14 days after return. Clinical suspicion guided further microbiological investigations. Among 765 enrolled participants, 310/765 (40.5%) had a clear source of infection (mainly traveler's diarrhea or respiratory infections), and 455/765 (59.5%) were categorized as AUFI. AUFI presented longer duration of fever ($p<0.001$), higher hospitalization ($p<0.001$) and ICU admission rates ($p<0.001$). Among travelers with AUFI, 132/455 (29.0%) had viral infections, including 108 arboviruses, 96/455 (21.1%) malaria and 82/455 (18.0%) bacterial infections. The majority of arboviral cases (80/108, 74.1%) was diagnosed between May and November. Dengue was the most frequent arbovirosis (92/108, 85.2%). After 1 month of follow-up, 136/455 (29.9%) patients with AUFI remained undiagnosed using standard diagnostic methods. No relevant differences in laboratory presentation were observed between undiagnosed and bacterial AUFI. Over 40% of returning travelers with AUFI were diagnosed with malaria or dengue, infections that can be easily diagnosed by rapid diagnostic tests. Arboviruses were the most common cause of AUFI (above malaria) and most cases were diagnosed during Aedes spp. high season. This is particularly relevant for those areas at risk of introduction of these pathogens. Empirical antibiotic regimens including doxycycline or azithromycin should be considered in patients with AUFI, after ruling out malaria and arboviruses.

Aedes albopictus Strain and Dengue Virus Serotype in the Dengue Fever Outbreaks in Japan: Implications of Wolbachia Infection.

Sasaki, T., Moi, M., Saito, K., Isawa, H., Takasaki, T., Sawabe, K.
31-08-2021
Jpn J Infect Dis
https://doi.org/10.7883/yoken.JJID.2021.376

From August 27 to October 15, 2014, a dengue fever outbreak with 158 autochthonous cases occurred after nearly 70 years of no reports of autochthonous cases in Japan. The most competent mosquito vector for dengue virus (DENV) transmission in Japan is Aedes albopictus. Since A. albopictus is widely distributed throughout Japan, we examined the susceptibility of this species to infection by DENV and the relationship of the endosymbiont Wolbachia (wAlbA and wAlbB) with susceptibility to DENV. The A. albopictus YYG strain, collected from the Yoyogi Park in 2014, the epicenter of the dengue fever outbreak, was found to have lower susceptibility to DENV 1 and 3 than that of the indigenous Japanese strains A. albopictus EBN 201808 (F1 from the field) and A. albopictus ISG 201603. Furthermore, the A. albopictus EBN 201808 strain showed the same susceptibility to DENV3 as the A. albopictus ISG 201603tet strain (Wolbachia-free). Susceptibility to DENV3 was not related to Wolbachia strains wAlbA or wAlbB in the A. albopictus ISG 201603 strain.

RAGE

Predictors of possible exposure to rabies in travellers: A case-control study.

Bantjes, S., Ruijs, W., van den Hoogen, G., Croughs, M., Pijtak, A., Sonder, G., Swaan, C., Haverkate, M.
27-03-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35354079

Timely administration of post-exposure prophylaxis (PEP) can prevent rabies. For non-vaccinated persons, PEP consists of multiple vaccinations and rabies immunoglobulin (RIG) on indication. Since RIG is scarce, the need for PEP could be restricted through preventing animal contact and pre-exposure vaccination. We aimed to identify determinants for possible rabies exposure among travellers to provide more targeted pre-travel advice. A case-control study was performed. Cases were defined as persons with a possible rabies exposure (category II or III injury according to WHO classification guidelines) in a rabies endemic country. Controls did not report exposure during travel. Multivariable logistic regression was performed. 229 cases and 1427 controls were included. Predictors ($p < 0.05$) of possible rabies exposure were young age, male sex, travelling to Western or Southeastern Asia, visiting a monkey park, pet ownership, previously visited the same country and considering oneself an experienced traveller. Negative predictors were travelling for business, visiting friends and relatives, and fear of animals. Pre-travel advice should take the identified predictors into account to provide better targeted information and pre-

exposure prophylaxis.

Serological survey of lyssaviruses in synanthropic bats and human exposure to bats in Slovakia.

Korytár, Ľ., Ondrejková, A., Drážovská, M., Zemanová, S., Prokeš, M.
21-02-2022
Ann Agric Environ Med
https://pubmed.ncbi.nlm.nih.gov/35352904

Bats are considered natural reservoirs for lyssaviruses. A total of 17 out of 19 known lyssaviruses circulate in bat populations. Lyssaviruses cause rabies in animals and humans. The transmission of lyssaviruses from European bats to terrestrial animals and humans is rare, but the risk of infection still exists even in developed countries. Slovakia is currently a rabies-free country. The aim of the study was to assess the potential circulation of EBLV-1 in synanthropic bats present in human inhabited buildings, and to give an overview of human exposure to bats. A passive serological survey targeted the prevalence of antibodies to bat lyssaviruses in synanthropic bats between 2009 - 2019. A total of 598 bats of the species *Pipistrellus pipistrellus*, *Pipistrellus pygmaeus*, *Eptesicus serotinus, Nyctalus noctula* and *Vespertilio murinus* were captured in buildings mainly in Eastern Slovakia, and examined by the rapid fluorescent focus inhibition test (RFFIT). Lyssavirus-specific antibodies were detected in 2 (0.3%) of the 598 examined bats. Additionally, brain tissues of bats found dead were examined using the standard fluorescent antibody test (FAT) with negative results. An overview of available data on human exposure to bats recorded in Slovakia from 2007 - 2019 is also included. The study confirmed the presence of lyssavirus antibodies in synanthropic bats in Slovakia, suggesting the active circulation of bat lyssaviruses in bat populations exploiting human buildings. Although the seroprevalence was found to be extremely low, the results show that any case of human exposure to bats must be treated with caution in order to protect public health.

A Country Classification System to Inform Rabies Prevention Guidelines and Regulations.

Henry, R., Blanton, J., Angelo, K., Pieracci, E., Stauffer, K., Jentes, E., Allen, J., Glynn, M., Brown, C., Friedman, C., Wallace, R.
26-03-2022
J Travel Med
https://pubmed.ncbi.nlm.nih.gov/35348741

Assessing the global risk of rabies exposure is a complicated task requiring individual risk assessments, knowledge of rabies epidemiology, surveillance capacity, and accessibility of rabies biologics on a national and regional scale. In many parts of the world, availability of this information is limited and when available is often dispersed across multiple sources. This hinders the process of making evidence-based health and policy recommendations to prevent the introduction and spread of rabies. CDC conducted a country-by-country qualitative assessment of risk and protective factors for rabies to develop an open-access database of core metrics consisting of the presence of Lyssaviruses (specifically canine or wildlife rabies virus variants or other bat Lyssaviruses), access to rabies immunoglobulins and vaccines, rabies surveillance capacity, and canine rabies control capacity. Using these metrics, we developed separate risk scoring systems to inform rabies prevention guidance for travelers and regulations for the importation of dogs. Both scoring systems assigned higher risk to countries with enzootic rabies (particularly canine rabies), and the risk scoring system for travelers also considered protective factors such as the accessibility of rabies biologics for postexposure prophylaxis. Cumulative scores were calculated across the assessed metrics to assign a risk value of low, moderate, or high. A total of 240 countries, territories, and dependencies were assessed, for travelers, 116 were identified as moderate to high risk and 124 were low or no risk; for canine rabies virus variant importation, 111 were identified as high-risk and 129 were low or no risk. We developed a comprehensive and easily accessible source of information for assessing the rabies risk for individual countries that included a database of rabies risk and protective factors based on enzootic status and availability of biologics, provided a resource that categorizes risk by country, and provided guidance based on these risk categories for travelers and importers of dogs into the United States.

Rapid processing of threatening faces in the amygdala of nonhuman primates: subcortical inputs and dual roles.

Inagaki, M., Inoue, K., Tanabe, S., Kimura, K., Takada, M., Fujita, I.
22-03-2022
Cereb Cortex
https://pubmed.ncbi.nlm.nih.gov/35323915

A subcortical pathway through the superior colliculus and pulvinar has been proposed to provide the amygdala with rapid but coarse visual information about emotional faces. However, evidence for short-latency, facial expression-discriminating responses from individual amygdala neurons is lacking; even if such a response exists, how it might contribute to stimulus detection is unclear. Also, no definitive anatomical evidence is available for the assumed pathway. Here we showed that ensemble responses of amygdala neurons in monkeys carried robust information about open-mouthed, presumably threatening, faces within 50 ms after stimulus onset. This short-latency signal was not found in the visual cortex, suggesting a subcortical origin. Temporal analysis revealed that the early response contained excitatory and suppressive components. The excitatory component may be useful for sending rapid signals downstream, while the sharpening of the rising phase of later-arriving inputs (presumably from the cortex) by the suppressive component might improve the processing of facial expressions over time. Injection of a retrograde trans-synaptic tracer into the amygdala revealed presumed monosynaptic labeling in the pulvinar and disynaptic labeling in the superior colliculus,

including the retinorecipient layers. We suggest that the early amygdala responses originating from the colliculo-pulvino-amygdalar pathway play dual roles in threat detection.

Rabies Virus Glycoprotein-Mediated Transportation and T Cell Infiltration to Brain Tumor by Magnetoelectric Gold Yarnballs.

Cheng, W., Su, Y., Hsu, H., Lin, Y., Chu, L., Huang, W., Lu, Y., Chiang, C., Hu, S.
28-02-2022
ACS Nano
https://doi.org/10.1021/acsnano.1c09601

T lymphocyte infiltration with immunotherapy potentially suppresses most devastating brain tumors. However, local immune privilege and tumor heterogeneity usually limit the penetration of immune cells and therapeutic agents into brain tumors, leading to tumor recurrence after treatment. Here, a rabies virus glycoprotein (RVG)-camouflaged gold yarnball (RVG@GY) that can boost the targeting efficiency at a brain tumor *via* dual hierarchy- and RVG-mediated spinal cord transportation, facilitating the decrease of tumor heterogeneity for T cell infiltration, is developed. Upon magnetoelectric irradiation, the electron current generated on the GYs activates the electrolytic penetration of palbociclib-loaded dendrimer (Den[Pb]) deep into tumors. In addition, the high-density GYs at brain tumors also induces the disruption of cell-cell interactions and T cell infiltration. The integration of the electrolytic effects and T cell infiltration promoted by drug-loaded RVG@GYs deep in the brain tumor elicits sufficient T cell numbers and effectively prolongs the survival rate of mice with orthotopic brain tumors.

Using social media listening and data mining to understand travellers' perspectives on travel disease risks and vaccine-related attitudes and behaviours.

Bravo, C., Castells, V., Zietek-Gutsch, S., Bodin, P., Molony, C., Frühwein, M.
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J Travel Med
https://pubmed.ncbi.nlm.nih.gov/35085399

Travellers can access online information to research and plan their expeditions/excursions, and seek travel-related health information. We explored German travellers' attitude and behaviour toward vaccination, and their travel-related health information seeking activities. We used two approaches: web 'scraping' of comments on German travel-related sites and an online survey. 'Scraping' of travel-related sites was undertaken using keywords/synonyms to identify vaccine- and disease-related posts. The raw unstructured text extracted from online comments was converted to a structured dataset using Natural Language Processing Techniques. Traveller personas were defined using K-means based on the online survey results, with cluster (i.e. persona) descriptions made from the most discriminant features in a distinguished set of observations. The web-scraped profiles were mapped to the personas identified. Travel and vaccine-related behaviours were described for each persona. We identified ~2.6 million comments; ~880 k were unique and mentioned ~280 k unique trips by ~65 k unique profiles. Most comments were on destinations in Europe (37%), Africa (21%), Southeast Asia (12%) and the Middle East (11%). Eight personas were identified: 'middle-class family woman', 'young woman travelling with partner', 'female globe-trotter', 'upper-class active man', 'single male traveller', 'retired traveller', 'young backpacker', and 'visiting friends and relatives'. Purpose of travel was leisure in 82-94% of profiles, except the 'visiting friends and relatives' persona. Malaria and rabies were the most commented diseases with 12.7 k and 6.6 k comments, respectively. The 'middle-class family woman' and the 'upper-class active man' personas were the most active in online conversations regarding endemic disease and vaccine-related topics, representing 40% and 19% of comments, respectively. Vaccination rates were 54%-71% across the traveller personas in the online survey. Reasons for vaccination reluctance included perception of low risk to disease exposure (21%), price (14%), fear of side effects (12%) and number of vaccines (11%). The information collated on German traveller personas and behaviours toward vaccinations should help guide counselling by healthcare professionals.

Long-term persistence of antibodies and boostability after rabies intradermal pre-exposure prophylaxis.

Mills, D., Lau, C., Mills, C., Furuya-Kanamori, L.
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J Travel Med
https://pubmed.ncbi.nlm.nih.gov/34875078

Currently, there is limited data on long-term persistence of antibodies and boostability of intradermal (ID) rabies pre-exposure prophylaxis (PrEP) schedules. This study investigated travellers who received a primary ID PrEP schedule at least 5 years previously to determine the persistence of antibodies and subsequent antibody response after one 0.1-ml ID booster dose. Adults (age≥18 years) who had previously received ID PrEP at a specialist travel medicine clinic in Brisbane, Australia were included. At Day 0, blood was collected for serology and one dose of 0.1-ml ID rabies vaccine (Verorab®) was administered. At Day 7, serology was repeated. At Day 14, participants were given results and enquired if they experienced adverse events following immunization (AEFIs). Antibodies were measured using Platelia Rabies II ELISA; levels ≥0.5 EU/mL were considered antibody-positive. 158 participants were included [64.6% female, median age at enrolment 56.4 years, interquartile range (IQR) 42.4-65.2 years], and median time since the primary ID PrEP was 8.5 years (IQR 6.9-11.7 years). The majority of participants (82.3%) were antibody-positive at Day 0. The proportion of participants who were antibody-positive at Day 0 was higher among those who were younger at primary vaccination (87.0% if aged<50 years, 75.8% of aged ≥50 years). The proportion of participants who were antibody-

positive declined as median time since primary vaccination increased, though the trend was not statistically significant (p-trend=0.187). All except one participant (99.4%) were antibody-positive after one ID booster dose. AEFIs were reported by 42.4% of participants and were mainly mild. Rabies antibodies persist for many years after ID PrEP and can be rapidly boosted with a single ID dose. Future studies are needed to confirm that ID PrEP primes the immune system sufficiently so that boosters are not routinely needed, and only given in the event of a rabies-prone exposure.

TRACHOME

Post-Validation Survey in Two Districts of Morocco after the Elimination of Trachoma as a Public Health Problem.

Hammou, J., Guagliardo, S., Obtel, M., Razine, R., Haroun, A., Youbi, M., Bellefquih, A., White, M., Gwyn, S., Martin, D.
28-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-1140

Trachoma is the leading infectious cause of blindness. In 2016, Morocco was validated by WHO as having eliminated trachoma as a public health problem. We evaluated two previously endemic districts in Morocco for trachomatous inflammation-follicular (TF), trachomatous trichiasis (TT), and antibodies against Chlamydia trachomatis, the causative agent of trachoma. Community-based cross-sectional surveys in the districts of Boumalene Dades and Agdez included 4,445 participants for whom both questionnaire and serology data were available; 58% were aged 1-9 years. Participants had eyes examined for TF and blood collected for analysis of antibodies to the C. trachomatis antigen Pgp3 by both a multiplex bead assay (MBA) and lateral flow assay (LFA). Seroconversion rates (SCR) per 100 people per year were used to estimate changes in the force of infection using Bayesian serocatalytic models. In Agdez, TF prevalence in 1-9-year-olds was 0.3%, seroprevalence ranged from 9.4% to 11.4%, and SCR estimates ranged from 2.4 to 3.0. In Boumalene Dades, TF prevalence in 1-9-year-olds was 0.07%, and modeling data from the different assays indicated a decrease in transmission between 20 and 24 years ago. The TF data support an absence of active trachoma in the two districts examined. However, seroprevalence and SCR in younger people were higher in Agdez than Boumalene Dades, showing that there can be differences in serology metrics in areas with similar TF prevalence. Data will be included in multicountry analyses to better understand potential thresholds for serological surveillance in trachoma.

Concordance of ompA types in children re-infected with ocular Chlamydia trachomatis following mass azithromycin treatment for trachoma.

Mosenia, A., Chin, S., Alemayehu, W., Melese, M., Lakew, T., Zhou, Z., Doan, T., Cevallos, V., Lietman, T., Keenan, J.
28-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010237

The chlamydial major outer membrane protein, encoded by the ompA gene, is a primary target for chlamydial vaccine research. However, human studies of ompA-specific immunity are limited, and prior studies have been limited in differentiating re-infection from persistent infection. The purpose of this study was to assess whether children living in trachoma-endemic communities with re-infections of ocular chlamydia were more likely to be infected with a different or similar genovar. The study included 21 communities from a trachoma-hyperendemic area of Ethiopia that had been treated with a mass azithromycin distribution for trachoma. Conjunctival swabbing was offered to all children younger than 5 years of age at baseline (i.e., pre-treatment), and then at follow-up visits 2 and 6 months later. Swabs were subjected to polymerase chain reaction (PCR) to detect C. trachomatis. A random sample of 359 PCR-positive swabs, stratified by study visit and study community, was chosen for ompA sequencing. In addition, ompA sequencing was performed on all swabs of 24 children who experienced chlamydial re-infection (i.e., positive chlamydial test before treatment, negative test 2 months following mass distribution of azithromycin, and again a positive test 6 months post-treatment). ompA sequencing was successful for 351 of 359 swabs of the random sample and 44 of 48 swabs of the re-infection sample. In the random sample, ompA types clustered within households more than would be expected by chance. Among the 21 re-infected children with complete ompA data, 14 had the same ompA type before and after treatment. The high frequency of ompA concordance suggests incomplete genovar-specific protective immunity and the need for multiple antigens as vaccine targets.

The Gambia has eliminated trachoma as a public health problem: Challenges and successes.

Aboe, A., Joof, B., Kanyi, S., Hydara, A., Downs, P., Bush, S., Courtright, P.
28-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010282

Trachoma is the leading infectious cause of blindness in the world and has been known to be a major public health problem in The Gambia for over 60 years. Nationwide blindness surveys, including trachoma, in 1986 and 1996 provided the foundation for a comprehensive plan to implement a trachoma elimination strategy. Impact and pre-validation surveillance surveys in 2011-13 demonstrated that active trachoma was below WHO threshold for elimination but trichiasis remained a public health problem. Trichiasis-only

surveys in 2019 demonstrated that trichiasis was below WHO thresholds for elimination and in 2020 the Government of The Gambia completed and submitted its dossier for validation of elimination as a public health problem. Challenges that The Gambia faced on the pathway to elimination included effective use of data for decision making, poor trichiasis surgical outcomes, lack of access to antibiotic treatment for low prevalence districts, high attrition of ophthalmic nurses trained as trichiasis surgeons, unexpected active trachoma in madrassas, the misalignment of elimination of active trachoma and trichiasis, trichiasis in urban settings, and maintaining the quality of surgery post-elimination when trichiasis cases are rare. Elimination of trachoma does not end with the submission of an elimination dossier; The Gambia will need to sustain monitoring and support over the coming years.

The economics of vision impairment and its leading causes: A systematic review.

Revue de littérature

Marques, A., Ramke, J., Cairns, J., Butt, T., Zhang, J., Jones, I., Jovic, M., Nandakumar, A., Faal, H., Taylor, H., Bastawrous, A., Braithwaite, T., Resnikoff, S., Khaw, P., Bourne, R., Gordon, I., Frick, K., Burton, M.
22-03-2022
EClinicalMedicine
https://doi.org/10.1016/j.eclinm.2022.101354

Vision impairment (VI) can have wide ranging economic impact on individuals, households, and health systems. The aim of this systematic review was to describe and summarise the costs associated with VI and its major causes. We searched MEDLINE (16 November 2019), National Health Service Economic Evaluation Database, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment database (12 December 2019) for partial or full economic evaluation studies, published between 1 January 2000 and the search dates, reporting cost data for participants with VI due to an unspecified cause or one of the seven leading causes globally: cataract, uncorrected refractive error, diabetic retinopathy, glaucoma, age-related macular degeneration, corneal opacity, trachoma. The search was repeated on 20 January 2022 to identify studies published since our initial search. Included studies were quality appraised using the British Medical Journal Checklist for economic submissions adapted for cost of illness studies. Results were synthesized in a structured narrative. Of the 138 included studies, 38 reported cost estimates for VI due to an unspecified cause and 100 reported costs for one of the leading causes. These 138 studies provided 155 regional cost estimates. Fourteen studies reported global data; 103/155 (66%) regional estimates were from high-income countries. Costs were most commonly reported using a societal ($n = 48$) or healthcare system perspective ($n = 25$). Most studies included only a limited number of cost components. Large variations in methodology and reporting across studies meant cost estimates varied considerably. The average quality assessment score was 78% (range 35-100%); the most common weaknesses were the lack of sensitivity analysis and insufficient disaggregation of costs. There was substantial variation across studies in average treatment costs per patient for most conditions, including refractive error correction (range $12-$201 ppp), cataract surgery (range $54-$3654 ppp), glaucoma (range $351-$1354 ppp) and AMD (range $2209-$7524 ppp). Future cost estimates of the economic burden of VI and its major causes will be improved by the development and adoption of a reference case for eye health. This could then be used in regular studies, particularly in countries with data gaps, including low- and middle-income countries in Asia, Eastern Europe, Oceania, Latin America and sub-Saharan Africa.

Ulcere de Buruli

Pian

Lepre

[Epidemiological behavior of leprosy in several Latin American countries, 2011-2020

Comportamento epidemiológico da hanseníase em vários países da América Latina, 2011-2020].

Cáceres-Durán, M.
23-03-2022
Rev Panam Salud Publica
https://doi.org/10.26633/RPSP.2022.14

To describe the epidemiological behavior of leprosy in several Latin American countries during 2011-2020, based on World Health Organization (WHO) indicators. Cross-sectional, descriptive and quantitative study with official data on incidence and prevalence in the general population, children, clinical form and cases with grade 2 disability from WHO records between 2011 and 2020. The eight countries in Latin America that reported most cases were selected and analyses were carried out using simple descriptive and comparative statistics between different variables. During the study period, 301 312 cases of leprosy were reported in the selected countries: Argentina, Brazil, Colombia, Cuba, Dominican Republic, Mexico, Paraguay, and Venezuela. Brazil is the only country in the region with a prevalence greater than 1 per 10 000, representing 93.77% of all cases. Brazil and the Dominican Republic showed an increase in prevalence during 2011-2019, while in other countries the trend was decreasing. The disease is more frequent in men, and multibacillary cases

significantly exceed paucibacillary ones. Brazil showed the highest incidences of cases of childhood leprosy and grade 2 disability during the evaluated period. In Latin America, leprosy is only considered a public health problem in Brazil; however, most countries in the region continue to report cases annually, revealing a lack of adequate medical care. This study confirmed the importance of active surveillance, early diagnosis and planning of actions against the disease in all the countries evaluated with the aim of reducing its transmission.

Community intervention programmes with people affected by leprosy: Listening to the voice of professionals.

Martos-Casado, G., Vives-Cases, C., Gil-González, D.
28-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010335

Community participation and implementing interventions based on the community are key strategies to eliminate leprosy. Health professionals have an essential role as they are a necessary source of information because of their knowledge and experience, as well as their comprehensive perspective of contexts included in the programmes. This study has the aim of analysing the perceptions on the development of programmes with people affected by leprosy from the perspective of professionals that work at different organisations in endemic contexts. A qualitative study was carried out with the written response to an open question questionnaire which was sent by email. The script content was related to positive aspects and difficulties in daily work, participation from the community in activities, contribution to gender equality and programme sustainability. 27 health professionals were interviewed, 14 women and 13 men, all of which belonged to 16 organisations in India and Brazil. Once the content of the interviews was analysed, two main topics emerged: barriers perceived by professionals and proposals to improve the sustainability of the programmes. Professionals identify barriers related to social stigma, inequalities, gender inequalities, difficulty managing the disease, limited services, lack of resources and lack of community participation. Furthermore, some necessary recommendations were taken into account to improve programme development related to: Eliminating stigma, reaching gender equality, developing adequate and effective services, guaranteeing adequate and quality resources and achieving compassion among professionals. Although introducing community programmes with people affected by leprosy has a long history in countries such as India and Brazil, there are still several barriers that can hinder their development. Based on the specific needs of the contexts, recommendations are suggested that, with the involvement of all parties and with sensitive approaches towards human rights and gender, they could help to guarantee universal health coverage and the sustainability of said programmes.

Dapsone Azo-Linked with Two Mesalazine Moieties Is a "Me-Better" Alternative to Sulfasalazine.

Kang, C., Kim, J., Ju, S., Park, S., Yoo, J., Yoon, I., Kim, M., Jung, Y.
21-03-2022
Pharmaceutics
https://pubmed.ncbi.nlm.nih.gov/35336057

Dapsone (DpS) is an antimicrobial and antiprotozoal agent, especially used to treat leprosy. The drug shares a similar mode of action with sulfonamides. Additionally, it possesses anti-inflammatory activity, useful for treating autoimmune diseases. Here, we developed a "me-better" alternative to sulfasalazine (SSZ), a colon-specific prodrug of mesalazine (5-ASA) used as an anti-inflammatory bowel diseases drug; DpS azo-linked with two molecules of 5-ASA (AS-DpS-AS) was designed and synthesized, and its colon specificity and anti-colitic activity were evaluated. AS-DpS-AS was converted to DpS and the two molecules of 5-ASA (up to approximately 87% conversion) within 24 h after incubation in the cecal contents. Compared to SSZ, AS-DpS-AS showed greater efficiency in colonic drug delivery following oral gavage. Simultaneously, AS-DpS-AS substantially limited the systemic absorption of DpS. In a dinitrobenzene sulfonic acid-induced rat colitis model, oral AS-DpS-AS elicited better efficacy against rat colitis than oral SSZ. Moreover, intracolonic treatment with DpS and/or 5-ASA clearly showed that combined treatment with DpS and 5-ASA was more effective against rat colitis than the single treatment with either DpS or 5-ASA. These results suggest that AS-DpS-AS may be a "me-better" drug of SSZ with higher therapeutic efficacy, owing to the combined anti-colitic effects of 5-ASA and DpS.

Musculoskeletal Manifestations of Leprosy.

Belani, P.
22-03-2022
Rheumatology (Oxford)
https://pubmed.ncbi.nlm.nih.gov/35323918

TB training in Kenya: building capacity for care and prevention.

Angala, P., Dlodlo, R., Wanjala, S., Mamo, G., Mugambi-Nyaboga, L., Onyango Okoth, E., Macharia, S., Maina, M., Wachira, S., Owuor, K., Masini, E., Wekesa, P., Carter, E., Mungai, B.
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Public Health Action
https://doi.org/10.5588/pha.21.0075

Devolution of healthcare services in Kenya resulted in a large number of newly recruited tuberculosis (TB) coordinators. We describe a unique collaboration between a national tuberculosis program (NTP), a local, and an international non-governmental organization to build human resource capacity in TB care and prevention. From 2016 to 2021, the Kenya Division of National Tuberculosis, Leprosy and Lung Disease Program, Centre for Health Solutions-Kenya, and the

International Union Against Tuberculosis and Lung Disease developed and conducted a series of 7-day training courses. A key focus of training was the introduction of TBData4Action, an approach involving the local use of routinely available data to strengthen decision-making and support supervision. Implementation outcomes included training 331 (96%) coordinators out of 344, representing all 47 counties, 37 national officers and 21 other stakeholders using the country-tailored curriculum, including hands-on group work by county teams and field practicals. Thirty-five national facilitators were identified and mentored as local faculty. Training costs were reduced by 75% compared with international alternatives. The collaboration resulted in the training of the majority of the coordinators in a standardized approach to TB care. A sustainable approach to capacity building in local data use was found feasible; the model could be adapted by other NTPs.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Proteolytic inhibitors as alternative medicines to treat trypanosomatid-caused diseases: experience with calpain inhibitors.

Ennes-Vidal, V., Dos Santos, A., Branquinha, M., d'Avila-Levy, C.
25-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35352772

The treatment for tropical neglected diseases, such as Chagas disease (CD) and leishmaniasis, is extremely limited to a handful of drugs that suffer from unacceptable toxicity, tough administration routes, like parenteral, and increasing treatment failures due to the parasite resistance. Consequently, there is urgency for the development of new therapeutic options to treat such diseases. Since peptidases from these parasites are responsible for crucial functions in their biology, these molecules have been explored as alternative targets. In this context, a myriad of proteolytic inhibitors has been developed against calcium-dependent cysteine-type peptidases, collectively called calpains, which are implicated in several human pathophysiological diseases. These molecules are highly expanded in the genome of trypanosomatids and they have been reported participating in several parasite biological processes. In the present perspective, we discuss our almost two decades of experience employing the calpain inhibitors as an interesting shortcut to a possible repurpose strategy to treat CD and leishmaniasis.

Kidney complications of parasitic diseases.

Revue de littérature

Daher, E., da Silva Junior, G., Trivedi, M., Fayad, T., Srisawat, N., Nair, S., Siriyasatien, P., de Lacerda, M., Baptista, M., Vankalakunti, M., Jha, V.
28-03-2022
Nat Rev Nephrol
https://doi.org/10.1038/s41581-022-00558-z

Parasitic agents have been known to cause human disease since ancient times and are endemic in tropical and subtropical regions. Complications of parasitic diseases, including kidney involvement, are associated with worse outcomes. Chagas disease, filariasis, leishmaniasis, malaria and schistosomiasis are important parasitic diseases that can damage the kidney. These diseases affect millions of people worldwide, primarily in Africa, Asia and Latin America, and kidney involvement is associated with increased mortality. The most common kidney complications of parasitic diseases are acute kidney injury, glomerulonephritis and tubular dysfunction. The mechanisms that underlie parasitic disease-associated kidney injury include direct parasite damage; immunological phenomena, including immune complex deposition and inflammation; and systemic manifestations such as haemolysis, haemorrhage and rhabdomyolysis. In addition, use of nephrotoxic drugs to treat parasitic infections is associated with acute kidney injury. Early diagnosis of kidney involvement and adequate management is crucial to prevent progression of kidney disease and optimize patient recovery.

COVID-19: an opportunity of systematic integration for Chagas disease. Example of a community-based approach within the Bolivian population in Barcelona.

Gómez I Prat, J., Essadek, H., Esperalba, J., Serrat, F., Guiu, I., Goterris, L., Zules-Oña, R., Choque, E., Pastoret, C., Ponces, N., de Los Santos, J., Pons, J., Dehousse, A., Albajar-Viñas, P., Pumarola, T., Campins, M., Sulleiro, E.
28-03-2022
BMC Infect Dis
https://doi.org/10.1186/s12879-022-07305-6

As a Neglected Tropical Disease associated with Latin America, Chagas Disease (CD) is little known in non-endemic territories of the Americas, Europe and Western Pacific, making its control challenging, with limited detection rates, healthcare access and consequent epidemiological silence. This is reinforced by its biomedical characteristics-it is usually asymptomatic-and the fact that it mostly affects people with low social and financial resources. Because CD is mainly a chronic infection, which principally causes a cardiomyopathy and can also cause a prothrombotic status, it increases the risk of contracting severe COVID-19. In order to get an accurate picture of CD and COVID-19 overlapping and co-infection, this operational research draws on community-based experience and participative-action-research components. It was conducted during the Bolivian elections in Barcelona on a representative sample of that community. The results show that 55% of the people interviewed had already undergone a previous T. cruzi infection screening-among which 81% were diagnosed in Catalonia and 19% in Bolivia. The prevalence of T. cruzi infection was 18.3% (with 3.3% of discordant results), the SARS-CoV-2 22.3% and the coinfection rate, 6%. The benefits

of an integrated approach for COVID-19 and CD were shown, since it only took an average of 25% of additional time per patient and undoubtedly empowered the patients about the co-infection, its detection and care. Finally, the rapid diagnostic test used for COVID-19 showed a sensitivity of 89.5%. This research addresses CD and its co-infection, through an innovative way, an opportunity of systematic integration, during the COVID-19 pandemic.

Evaluation of Four Biomarkers in Patients Chronically Infected with Trypanosoma cruzi and Their Relationship with Disease Progression.

Luquetti, A., de Oliveira, D., do Nascimento Tavares, S., de Oliveira, E.
28-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-0620

This study evaluated four biomarkers of inflammation or fibrosis as progression indicators for heart disease in patients with Chagas disease. We compared values of these markers at the time of the first sample collection of blood (first time point) and at the time of the last collection of blood (second time point) for 103 individuals positive for Trypanosoma cruzi antibodies. They were split into two clinical groups: 52 individuals with the indeterminate form of the disease at the first time point and 51 controls that already had either cardiac involvement (N = 25) or megaviscera (megaesophagus and/or megacolon; N = 26) at that time. All individuals had an electrocardiogram performed both at the first and second time point (mean time between time points: 11 years). All samples were blind tested for galectin-3, brain natriuretic peptide (NT-proBNP), lysyl oxidase-like protein 2 (LOXL2), and troponin. Differences in concentrations between samples were analyzed using the months between samples as the covariate. This analysis showed that values for all markers, except troponin biomarkers had a significative increase at the second time point for the 91 patients without progression. A similar result was obtained for NT-proBNP and LOXL2 with sera from 12 patients that progressed with cardiac disease. The single marker that showed a significative difference between groups (P = 0.01) was galectin-3. We concluded that galectin-3 was the only marker with a prognostic value in relation to the progression or worsening of heart disease in patients with Chagas disease.

Population Pharmacodynamic Modeling of Eflornithine-Based Treatments Against Late-Stage Gambiense Human African Trypanosomiasis and Efficacy Predictions of L-eflornithine-Based Therapy.

Amilon, C., Boberg, M., Tarning, J., Äbelö, A., Ashton, M., Jansson-Löfmark, R.
25-03-2022
AAPS J
https://doi.org/10.1208/s12248-022-00693-2

Eflornithine is a recommended treatment against late-stage gambiense human African trypanosomiasis, a neglected tropical disease. Standard dosing of eflornithine consists of repeated intravenous infusions of a racemic mixture of L- and D-eflornithine. Data from three clinical studies, (i) eflornithine intravenous monotherapy, (ii) nifurtimox-eflornithine combination therapy, and (iii) eflornithine oral monotherapy, were pooled and analyzed using a time-to-event pharmacodynamic modeling approach, supported by in vitro activity data of the individual enantiomers. Our aim was to assess (i) the efficacy of the eflornithine regimens in a time-to-event analysis and (ii) the feasibility of an L-eflornithine-based therapy integrating clinical and preclinical data. A pharmacodynamic time-to-event model was used to estimate the total dose of eflornithine, associated with 50% reduction in baseline hazard, when administered as monotherapy or in the nifurtimox-eflornithine combination therapy. The estimated total doses were 159, 60 and 291 g for intravenous eflornithine monotherapy, nifurtimox-eflornithine combination therapy and oral eflornithine monotherapy, respectively. Simulations suggested that L-eflornithine achieves a higher predicted median survival, compared to when racemate is administered, as treatment against late-stage gambiense human African trypanosomiasis. Our findings showed that oral L-eflornithine-based monotherapy would not result in adequate efficacy, even at high dose, and warrants further investigations to assess the potential of oral L-eflornithine-based treatment in combination with other treatments such as nifurtimox. An all-oral eflornithine-based regimen would provide easier access to treatment and reduce burden on patients and healthcare systems in gambiense human African trypanosomiasis endemic areas. Graphical abstract.

Mitigation of benznidazole toxicity and oxidative stress following ascorbic acid supplementation in an adult traveller with chronic indeterminate Chagas' disease.

Van Den Broucke, S., Van Herreweghe, M., Breynaert, A., Van Esbroeck, M., Truyens, C., De Bruyne, T., Hermans, N., Huits, R.
24-03-2022
J Antimicrob Chemother
https://pubmed.ncbi.nlm.nih.gov/35325159

Benznidazole is an effective drug in the trypanocidal treatment of acute and chronic indeterminate Chagas' disease (CD). However, adverse drug reactions (ADR) are common and frequently cause patients to discontinue treatment. We hypothesized that antioxidant supplementation could mitigate benznidazole-induced toxicity. We co-supplemented an adult traveller with chronic indeterminate CD who experienced benznidazole ADR with ascorbic acid (AA), 1000 mg/day. We measured selected serum biomarkers of oxidative stress [total antioxidant status (TAS), total oxidative status (TOS), nuclear factor erythroid 2-related factor 2 (Nrf2), malondialdehyde (MDA), extracellular glutathione peroxidase (GPX3), catalase (CAT) and total superoxide dismutase (T-SOD)] at timepoints

before and throughout benznidazole treatment and after AA co-supplementation. AA co-supplementation effectively mitigated benznidazole-induced ADR during the aetiological treatment of chronic indeterminate CD. The kinetics of serum biomarkers of oxidative stress suggested significantly decreased oxidative insult in our patient. We hypothesize that the key pathophysiological mechanism of benznidazole-associated toxicity is oxidative stress, rather than hypersensitivity. AA co-supplementation may improve adherence to benznidazole treatment of chronic indeterminate (or acute) CD. Oxidative stress biomarkers have the potential to guide the clinical management of CD. Prospective studies are needed to establish the benefit of antioxidant co-supplementation to benznidazole treatment of CD in reducing benznidazole toxicity, parasite clearance and the prevention of end-organ damage.

Multi-therapeutic strategy targeting parasite and inflammation-related alterations to improve prognosis of chronic Chagas cardiomyopathy: a hypothesis-based approach.

Lannes-Vieira, J.
23-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35320825

Chagas disease (CD), caused by infection by the protozoan parasite Trypanosoma cruzi, presents as main clinical manifestation the chronic chagasic cardiomyopathy (CCC). CCC afflicts millions of people, mostly in Latin America, and vaccine and effective therapy are still lacking. Comprehension of the host/parasite interplay in the chronic phase of T. cruzi infection may unveil targets for rational trait-based therapies to improve CCC prognosis. In the present viewpoint, I critically summarise a collection of data, obtained by our network of collaborators and other groups on CCC and preclinical studies on pathogenesis, targeting identification for intervention and the use of drugs with immunomodulatory properties to improve CCC. In the last two decades, models combining mouse lineages and T. cruzi strains allowed replication of crucial clinical, histopathological, and immunological traits of CCC. This condition includes conduction changes (heart rate changes, arrhythmias, atrioventricular blocks, prolongation of the QRS complex and PR and corrected QT intervals), ventricular dysfunction and heart failure, CD8-enriched myocarditis, tissue remodeling and progressive fibrosis, and systemic inflammatory profile, resembling "cytokine storm". Studies on Chagas' heart disease pathogenesis begins to unveil the molecular mechanisms underpinning the inflammation-related cardiac tissue damage, placing IFNγ, TNF and NFκB signaling as upstream regulators of miRNAs and mRNAs associated with critical biological pathways as cell migration, inflammation, tissue remodeling and fibrosis, and mitochondrial dysfunction. Further, data on preclinical trials using hypothesis-based tools, targeting parasite and inflammation-related alterations, opened paths for multi-therapeutic approaches in CCC. Despite the long path taken using experimental CD models replicating relevant aspects of CCC and testing new therapies and therapeutic schemes, these findings may get lost in translation, as conceptual and economical challenges, underpinning the valley of death across preclinical and clinical trials. It is hoped that such difficulties will be overcome in the near future.

Translational research in Chagas disease: perspectives in nutritional therapy emerging from selenium supplementation studies as a complementary treatment.

Revue de littérature

Araujo-Jorge, T., Ferreira, R.
21-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35319676

Translational research (TR) is an interdisciplinary branch of the biomedical field that seeks to connect its three supporting pillars: basic research on the bench, the hospital beds and other health system services, and the delivery of products for the well-being and health of the community. Here, we review the five transition stages of the TR spectrum, registering the lessons learned during > 20 years leading to the first clinical trial designed and performed in Brazil for testing a complementary treatment for Chagas disease (CD): the selenium trial (STCC). Lessons learned were: (1) to consider all the TR spectrum since the beginning of the project; (2) to start simultaneously animal studies and translation to humans; (3) to ensure a harmonious interaction between clinical and basic research teams; (4) to include MSc and PhD students only in pre-clinical and basic studies (TR0) or vertical clinical studies using retrospective samples and data (TR1); (5) to identify potential suppliers in the national commercial market for a future final treatment since the pre-clinical stage; (6) to keep an international network of experts as permanent advisers on the project. In the whole process, some perspectives were created: a complementary clinical trial for the opened questions and the construction of a Brazilian clinical CD platform.

LEISHMANIOSE

Thymic changes due to leishmaniasis in dogs: An immunohistochemical study.

Jussiani, G., Março, K., Bertolo, P., de Oliveira Vasconcelos, R., Machado, G.
24-03-2022
Vet Immunol Immunopathol
https://pubmed.ncbi.nlm.nih.gov/35358749

The thymus is necessary for the differentiation of T cells, a process that is regulated by the type of antigens found in thymocytes, the environment of surrounding cells and the thymus architecture. There is evidence that infectious

diseases may result in morphological changes in this organ, such as premature atrophy and decreased thymocyte proliferation, that can affect the immune response. We characterised the morphology and tissue distribution of haematopoietic and stromal cells in the thymuses of dogs naturally infected with Leishmania infantum, with the aim to determine the changes that may contribute to the pathophysiology of the disease. Thymus samples were collected from 15 animals (aged 6 months to 5 years) ELISA-positive for leishmaniasis and from 10 dogs from non-endemic regions for leishmaniasis whose death was not related to infectious causes. The samples were submitted to histological processing and staining with Haematoxylin-Eosin to assess thymic morphometry and histopathological changes. Masson's trichrome staining was used to quantify the connective tissue present (collagen). The immunohistochemical method was used to determine the cellular constitution of the thymus, using antibodies that aimed at marking T lymphocytes (anti-CD3), B lymphocytes (anti-CD79a), macrophages (anti-MAC387), mesenchymal cells (anti-vimentin), epithelial cells (anti-cytokeratin), cells in mitosis (anti-Ki67) and cells in apoptosis (anti-caspase-3). The histopathological evaluation of infected dogs showed more signs consistent with thymus atrophy, including decreased parenchyma, infiltration of adipose and connective tissue near the capsule and between the lobules, lymphoid rarefaction mainly in the cortical region and loss of the cortical-medullary demarcation. In addition, we observed a decrease in the amounts of CD3 + T lymphocytes, macrophages (MAC387) and Ki67-positive cells and an increase in the number of cells positive for cytokeratin and CD79a (B lymphocytes). Finally, the parasite was detected in 46% of infected thymuses and may contribute for the observed changes. Apparently, leishmaniasis, like other infectious diseases, causes atrophy of the thymus and depletion of thymocytes with a relative increase in thymus epithelial cells. These morphological changes in the normal organisation of the thymus by mechanisms not yet well known may result in the abnormal release of T cells, with consequent damage to the host's immune response.

Proteolytic inhibitors as alternative medicines to treat trypanosomatid-caused diseases: experience with calpain inhibitors.

Ennes-Vidal, V., Dos Santos, A., Branquinha, M., d'Avila-Levy, C.
25-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35352772

The treatment for tropical neglected diseases, such as Chagas disease (CD) and leishmaniasis, is extremely limited to a handful of drugs that suffer from unacceptable toxicity, tough administration routes, like parenteral, and increasing treatment failures due to the parasite resistance. Consequently, there is urgency for the development of new therapeutic options to treat such diseases. Since peptidases from these parasites are responsible for crucial functions in their biology, these molecules have been explored as alternative targets. In this context, a myriad of proteolytic inhibitors has been developed against calcium-dependent cysteine-type peptidases, collectively called calpains, which are implicated in several human pathophysiological diseases. These molecules are highly expanded in the genome of trypanosomatids and they have been reported participating in several parasite biological processes. In the present perspective, we discuss our almost two decades of experience employing the calpain inhibitors as an interesting shortcut to a possible repurpose strategy to treat CD and leishmaniasis.

Acoustophoretic Motion of Leishmania spp. Parasites.

Jiménez, A., Cabezas, D., Delay, M., Gómez, I., Camacho, M.
26-03-2022
Ultrasound Med Biol
https://pubmed.ncbi.nlm.nih.gov/35351318

The analysis of cell motion in an acoustic field is of interest as it can lead to new methods of cell separation, isolation and manipulation for diagnosis and treatment of diseases. Studies of the motion of different species of Leishmania parasites during exposure to ultrasonic standing waves in a microfluidic device allowed identification of acoustic responses of these parasites in their promastigote and amastigote forms. Both forms exhibited a positive acoustic contrast factor and were driven toward the pressure node established in the center of the channel by the acoustically induced radiation force (F_R). Promastigotes experience calculated F_R amplitudes one order of magnitude larger than those experienced by amastigotes because of the measured differences in volume. The aggregates formed at the pressure node have distinct shapes and stability conditions, for both promastigotes and amastigotes.

Chimeric virus-like particles presenting tumour-associated MUC1 epitope result in high titers of specific IgG antibodies in the presence of squalene oil-in-water adjuvant: towards safe cancer immunotherapy.

Panasiuk, M., Zimmer, K., Czarnota, A., Narajczyk, M., Peszyńska-Sularz, G., Chraniuk, M., Hovhannisyan, L., Żołędowska, S., Nidzworski, D., Żaczek, A., Gromadzka, B.
27-03-2022
J Nanobiotechnology
https://doi.org/10.1186/s12951-022-01357-1

Immunotherapy is emerging as a powerful treatment approach for several types of cancers. Modulating the immune system to specifically target cancer cells while sparing healthy cells, is a very promising approach for safer therapies and increased survival of cancer patients. Tumour-associated antigens are favorable targets for cancer immunotherapy, as they are exclusively expressed by the cancer cells, minimizing the risk of an autoimmune reaction. The ability to initiate the activation of the immune system can be achieved by virus-like particles (VLPs) which are safe and potent delivery tools. VLP-based vaccines have evolved dramatically over the last few

decades and showed great potential in preventing infectious diseases. Immunogenic potency of engineered VLPs as a platform for the development of effective therapeutic cancer vaccines has been studied extensively. This study involves recombinant VLPs presenting multiple copies of tumour-specific mucin 1 (MUC1) epitope as a potentially powerful tool for future immunotherapy. In this report VLPs based on the structural protein of Norovirus (NoV VP1) were genetically modified to present multiple copies of tumour-specific MUC1 epitope on their surface. Chimeric MUC1 particles were produced in the eukaryotic Leishmania tarentolae expression system and used in combination with squalene oil-in-water emulsion MF59 adjuvant to immunize BALB/c mice. Sera from vaccinated mice demonstrated high titers of IgG and IgM antibodies which were specifically recognizing MUC1 antigen. The obtained results show that immunization with recombinant chimeric NoV VP1- MUC1 VLPs result in high titers of MUC1 specific IgG antibodies and show great therapeutic potential as a platform to present tumour-associated antigens.

Barriers to cutaneous leishmaniasis care faced by indigenous communities of rural areas in Colombia: a qualitative study.

Bautista-Gomez, M., Doerfler, J., Del Mar Castro, M.
28-03-2022
BMC Infect Dis
https://doi.org/10.1186/s12879-022-07204-w

Neglected tropical diseases (NTDs) such as cutaneous leishmaniasis (CL) are often associated with rural territories and vulnerable communities with limited access to health care services. The objective of this study is to identify the potential determinants of CL care management in the indigenous communities in the rural area of the municipality of Pueblo Rico, through a people-centered approach. To achieve this goal, qualitative ethnographic methods were used, and a coding framework was developed using procedures in accordance with grounded theory. Three dimensions that affect access to health care for CL in this population were identified: (1) contextual barriers related to geographic, economic and socio-cultural aspects; (2) health service barriers, with factors related to administration, insufficient health infrastructure and coverage, and (3) CL treatment, which covers perceptions of the treatment and issues related to the implementation of national CL treatment guidelines. This study identified barriers resulting from structural problems at the national level. Moreover, some requirements of the national guidelines for CL management in Colombia impose barriers to diagnosis and treatment. We furthermore identified cultural barriers that influence the perceptions and behavior of the community and health workers. While the determinants to CL management are multidimensional, the most important barrier is the inaccessibility to CL treatment to the most vulnerable populations and its inadequacy for the socio-territorial setting, as it is not designed around the people, their needs and their context.

Kidney complications of parasitic diseases.

Revue de littérature

Daher, E., da Silva Junior, G., Trivedi, M., Fayad, T., Srisawat, N., Nair, S., Siriyasatien, P., de Lacerda, M., Baptista, M., Vankalakunti, M., Jha, V.
28-03-2022
Nat Rev Nephrol
https://doi.org/10.1038/s41581-022-00558-z

Parasitic agents have been known to cause human disease since ancient times and are endemic in tropical and subtropical regions. Complications of parasitic diseases, including kidney involvement, are associated with worse outcomes. Chagas disease, filariasis, leishmaniasis, malaria and schistosomiasis are important parasitic diseases that can damage the kidney. These diseases affect millions of people worldwide, primarily in Africa, Asia and Latin America, and kidney involvement is associated with increased mortality. The most common kidney complications of parasitic diseases are acute kidney injury, glomerulonephritis and tubular dysfunction. The mechanisms that underlie parasitic disease-associated kidney injury include direct parasite damage; immunological phenomena, including immune complex deposition and inflammation; and systemic manifestations such as haemolysis, haemorrhage and rhabdomyolysis. In addition, use of nephrotoxic drugs to treat parasitic infections is associated with acute kidney injury. Early diagnosis of kidney involvement and adequate management is crucial to prevent progression of kidney disease and optimize patient recovery.

Modeling and analysis of a fractional anthroponotic cutaneous leishmania model with Atangana-Baleanu derivative.

Haq, I., Khan, A., Ahmad, S., Ali, A., Rahman, M.
28-03-2022
Comput Methods Biomech Biomed Engin
https://doi.org/10.1080/10255842.2022.2035372

Very recently, Atangana and Baleanu defined a novel arbitrary order derivative having a kernel of non-locality and non-singularity, known as *AB* derivative. We analyze a non-integer order Anthroponotic Leshmania Cutaneous (ACL) problem exploiting this novel *AB* derivative. We derive equilibria of the model and compute its threshold quantity, i.e. the so-called reproduction number. Conditions for the local stability of the no-disease as well as the disease endemic states are derived in terms of the threshold quantity. The qualitative analysis for solution of the proposed problem have derived with the aid of the theory of fixed point. We use the predictor corrector numerical approach to solve the proposed fractional order model for approximate solution. We also provide, the numerical simulations for each of the compartment of considered model at different fractional orders along with comparison with integer order to elaborate the importance of modern derivative. The fractional investigation shows that the non-integer order derivative is more realistic about the inner dynamics of the Leishmania model lying between integer order.

Involvement of Akt and the antiapoptotic protein Bcl-xL in the inhibition of apoptosis of dendritic cells by Leishmania mexicana.

Rodríguez-González, J., Wilkins-Rodríguez, A., Gutiérrez-Kobeh, L.
27-03-2022
Parasite Immunol
https://doi.org/10.1111/pim.12917

The intracellular parasite Leishmania mexicana inhibits camptothecin (CPT)-induced apoptosis of monocyte-derived dendritic cells (moDC) through the down-regulation of p38 and JNK phosphorylation, while the kinase Akt is maintained active for 24 hours. In addition, the infection of moDC with L. mexicana promastigotes increases the protein presence of the antiapoptotic protein Bcl-xL. In the present work we aimed to investigate the role of Akt in the inhibition of apoptosis of moDC by L. mexicana and in the modulation of the expression of the antiapoptotic proteins Bcl-2, Mcl-1, and Bcl-xL. moDC were infected with L. mexicana metacyclic promastigotes and treated with CPT, an Akt inhibitor, or both and the MOMP and protein presence of active caspase 3, Bcl-2, Mcl-1, and Bcl-xL were evaluated. Our results show that the specific inhibition of Akt reverts the apoptosis protective effect exerted by L. mexicana on moDC reflected by a reduction in MOMP, caspase 3 activation, and upregulation of Bcl-xL. Interestingly, we also found that the infection of moDC with L. mexicana promastigotes induces a decrease in Bcl-2 along with an isoform change of Mcl-1, this independently to Akt activity. We demonstrated that Akt is deeply involved in the inhibition of apoptosis of moDC by L. mexicana.

About gladiators and a sacred disease.

Kattner, A.
23-03-2022
Biomed J
https://pubmed.ncbi.nlm.nih.gov/35339730

In this special edition of the Biomedical Journal the reader gains an insight into drug-resistant epilepsy and according treatment approaches involving deep brain stimulation, the ketogenic diet and fecal microbiota transplant. Another emphasis is put on personalized medicine strategies, and covered in articles about the use of natriuretic peptides against cancer, along with an article about companion diagnostics involving extracellular vesicles. Recurrent infection with C. difficile, associated risk factors and therapeutic options are discussed. We learn about a mechanism that helps Leishmania evade a host control mechanism, receive an update about human adenovirus and are presented with characteristic magnetic resonance neuroimaging in COVID-19 pediatric patients. An advanced assessment in pediatric septic shock and an improved model for a pediatric early warning system are proposed. Some of the genetic causes of renal hypomagnesemia are explored, the impact of air pollution on children is examined, and an antisiphon device is described for surgical treatment of hydrocephalus. The relation between energy metabolism, circadian rhythm and its influence on the ATPase in the SCN are investigated, and among others some of the genetics influencing smoking duration and lung cancer. Finally it is discussed how embryo quality can be improved in in vitro fertilization, and what impact high estradiol has on blastocyst implantation. The outcome of surgery to correct mandibular deficiency is assessed, and in two letters the inclusion of observational studies in the evaluation of clinical trials related to COVID-19 is elaborated.

Performance assessment of a new indirect rapid diagnostic test for plague detection in humans and other mammalian hosts.

Bezerra, M., Dos Santos, W., Rocha, I., Nadaes, N., Dantas-Torres, F., Sales, K., de Melo Neto, O., Sobreira, M., Silva, E., de Almeida, A., Reis, C.
24-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35339434

Plague is a flea-borne zoonosis that affects a wide range of mammals and still causes outbreaks in human populations yearly across several countries. While crucial for proper treatment, early diagnosis is still a major challenge in low- and middle-income countries due to poor access to laboratory infrastructure in rural areas. To tackle this issue, we developed and evaluated a new Fraction 1 capsular antigen (F1)-based rapid diagnostic test (RDT) as an alternative method for plague serological diagnosis and surveillance in humans and other mammals. In this study, 187 serum samples from humans, dogs, rodents and rabbits were retrospectively assessed using the plague RDT method. To calculate its performance, results were compared to those obtained by traditional hemagglutination (HA) and ELISA, which are well-established methods in the plague routine serodiagnosis. Remarkably, the results from RDT were in full agreement with those from the ELISA and HA assays, resulting in 100% (CI 95% = 95.5-100%) of sensitivity and 100% (CI 95% = 96.6-100%) of specificity. Accordingly, the Cohen's Kappa test coefficient was 1.0 (almost perfect agreement). Moreover, the RDT showed no cross-reaction when tested with sera from individuals positive to other pathogens, such as Y. pseudotuberculosis, Yersinia enterocolitica, Anaplasma platys, Ehrlichia canis and Leishmania infantum. Although preliminary, this study brings consistent proof-of-concept results with high performance of the Plague RDT when compared to HA and ELISA. Although further human and animal population-based studies will be necessary to validate these findings, the data presented here show that the plague RDT is highly sensitive and specific, polyvalent to several mammal species and simple to use in field surveillance or point-of-care situations with instant results.

Recombinant guanosine-5'-triphosphate (GTP)-binding protein associated with Poloxamer 407-based polymeric micelles protects against Leishmania infantum infection.

Lage, D., Machado, A., Vale, D., Freitas, C., Linhares, F., Cardoso,

J., Pereira, I., Ramos, F., Tavares, G., Ludolf, F., Oliveira-da-Silva, J., Bandeira, R., Silva, A., Simões, L., Reis, T., Oliveira, J., Christodoulides, M., Chávez-Fumagalli, M., Roatt, B., Martins, V., Coelho, E.
23-03-2022
Cytokine
https://pubmed.ncbi.nlm.nih.gov/35339043

Leishmania virulence proteins should be considered as vaccine candidates against disease, since they are involved in developing infection in mammalian hosts. In a previous study, a Leishmania guanosine-5'-triphosphate (GTP)-binding protein was identified as a potential parasite virulence factor. In the present work, the gene encoding GTP was cloned and the recombinant protein (rGTP) was evaluated as a vaccine candidate against Leishmania infantum infection. The protein was associated with saponin (rGTP/Sap) or Poloxamer 407-based micelles (rGTP/Mic) as adjuvants, and protective efficacy was investigated in BALB/c mice after parasite challenge. Both rGTP/Sap and rGTP/Mic compositions induced a Th1-type immune response in vaccinated animals, with significantly higher levels of IFN-γ, IL-12, IL-2, TNF-α, GM-CSF, nitrite, specific IgG2a isotype antibody and positive lymphoproliferation, when compared to the control groups. This response was accompanied by significantly lower parasite load in the spleens, livers, bone marrows and draining lymph nodes of the animals. Immunological and parasitological evaluations indicated that rGTP/Mic induced a more polarized Th1-type response and higher reduction in the organ parasitism, and with lower hepatotoxicity, when compared to the use of rGTP/Sap. In conclusion, our preliminary data suggest that rGTP could be considered for further development as a vaccine candidate to protect against VL.

In vitro antileishmanial activity of sustainable anacardic acid and cardol based silver nanoparticles on L. braziliensis.

Teixeira Bezerra, T., Oliveira de Almeida, M., Maria de Amorim Lima, N., Lúcia de Castro Rodrigues, N., Gomes Pereira Ribeiro, V., Jania Teixeira, M., Carbone, L., Mele, G., Lomonaco, D., Elaine Mazzetto, S.
23-03-2022
Int J Pharm
https://pubmed.ncbi.nlm.nih.gov/35337904

The search for effective and less toxic drugs for the treatment of Cutaneous Leishmaniasis (CL) is desirable due to the emergence of resistant parasites. The present study shows the preparation, characterization and in vitro antileishmanial activity of green-based silver nanoparticles (AgNPs) with Cashew Nutshell Liquid (CNSL, main constituents: anacardic acid (AA) and cardol (CD). The synthesis of silver nanoparticles was achieved by reduction with sodium borohydride in the presence of anacardic acid or cardol under microwave irradiation (400 W, 60 °C, 5 min) resulting in AgAA and AgCD. In vitro assay showed opposite effects for AgAA and AgCD. While AgAA is highly toxic to macrophages (CC_{50} = 6.910 µg mL^{-1}) and almost non-toxic for L.braziliensis (IC_{50} = 86.61 µg mL^{-1}), AgCD results very selective toward killing the parasite (CC_{50} = 195.0 µg mL^{-1}, IC_{50} = 11.54 µg mL^{-1}). AA's higher polarity and conical shape easily promote cell lysis by increasing cell permeability, while CD has a protective effect: for that reason, AA and AgAA were not further used for tests. CD (EC_{50} = 2.906 µg mL^{-1}) had higher ability to kill intracellular amastigotes than AgCD (EC_{50} = 16.00 µg mL^{-1}), however, less intact cells were seen on isolated CD tests. In addition, considering that NO is one of the critical molecular species for the intracellular control of Leishmania, we used Griess colorimetric test to analyze the effect of treatment with AgCD and CD. Overall, the in vitro antileishmanial tests indicate that AgCD should be further explored as a promising non-toxic treatment for CL.

Pentoxifylline in the Treatment of Cutaneous Leishmaniasis: A Randomized Clinical Trial in Colombia.

Castro, M., Cossio, A., Navas, A., Fernandez, O., Valderrama, L., Cuervo-Pardo, L., Marquez-Oñate, R., Gómez, M., Saravia, N.
21-03-2022
Pathogens
https://pubmed.ncbi.nlm.nih.gov/35335703

Addition of the immunomodulator pentoxifylline (PTX) to antimonial treatment of mucosal leishmaniasis has shown increased efficacy. This randomized, double-blind, placebo-controlled trial evaluated whether addition of pentoxifylline to meglumine antimoniate (MA) treatment improves therapeutic response in cutaneous leishmaniasis (CL) patients. Seventy-three patients aged 18-65 years, having multiple lesions or a single lesion ≥ 3 cm were randomized to receive: intramuscular MA (20 mg/kg/day × 20 days) plus oral PTX 400 mg thrice daily (intervention arm, *n* = 36) or MA plus placebo (control arm, *n* = 37), between 2012 and 2015. Inflammatory gene expression was evaluated by RT-qPCR in peripheral blood mononuclear cells from trial patients, before and after treatment. Intention-to-treat failure rate was 35% for intervention vs. 25% for control (OR: 0.61, 95% CI: 0.21-1.71). Per-protocol failure rate was 32% for PTX, and 24% for placebo (OR: 0.50, 95% CI: 0.13-1.97). No differences in frequency or severity of adverse events were found (PTX = 142 vs. placebo = 140). Expression of inflammatory mediators was unaltered by addition of PTX to MA. However, therapeutic failure was associated with significant overexpression of *il1β* and *ptgs2* (*p* < 0.05), irrespective of study group. No clinical benefit of addition of PTX to standard treatment was detected in early mild to moderate CL caused by *Leishmania* (*V.*) *panamensis*.

Pharmacokinetic study of AmB-NP-GR: A new granule form with amphotericin B to treat leishmaniasis and fungal infections.

Tadini, M., Fernandes, F., Ozelin, S., de Melo, M., Mansur, A., de Toledo, T., de Albuquerque, N., Tavares, D., Marquele-Oliveira, F., de Oliveira, A.
22-03-2022
Eur J Pharm Sci

https://pubmed.ncbi.nlm.nih.gov/35331860

Amphotericin B (AmB) has been the gold standard to treat systemic fungal infections. The use of AmB is restricted to hospitals because it poses several risks, mainly risks related to its high nephrotoxicity. Given the importance of this drug in medicine, new therapeutics and AmB formulations with nanotechnological improvements are required and could bring many benefits to patients. A new drug formulation with gastro-resistant coated granules has been proposed. The lipid-based system containing AmB was produced and used as raw material in the granulation/coated process. The new developed formulation (AmB-NP-GR) was characterized by optical microscopy, granulometry, and atomic force microscopy (AFM) after disintegration test. AmB-NP-GR showed granular shape, with most granules measured between 250 and 500 µm (37 ± 7% w/w). The AFM images indicated that the granule formulation should disintegrate in the intestine, to release the lipid-based carriers, making them available for absorption and allowing them to reach the blood circulation. The developed formulation was administered to rats in a single dose of 4.0 or 8.0 mg kg^{-1} and the pharmacokinetics was studied. The samples were analyzed by liquid chromatography coupled to mass spectrometry. Before the pharmacokinetic studies were conducted, the bioanalytical method was validated according to the EMA guideline and all evaluated parameters agreed with this guideline. The pharmacokinetic results showed that C_{max} was similar for both doses and that t_{max} was reached at 4-12 h for dose of 4.0 mg kg^{-1} and 4 h for dose of 8.0 mg kg^{-1}. The half-life related to the dose of 8.0 mg kg^{-1} increased significantly compared to the dose of 4.0 mg kg^{-1} (an increase of more than 3 times). In addition, the mean residence time related to the dose of 8.0 mg kg^{-1} was 4 times higher than for the lower dose. The clearance value showed to be higher for the lower dose. Together, these results provide important conclusions for experimental design of other in vivo safety and efficacy studies of AmB-NP-GR.

Influence of the presence of mannose-binding lectin polymorphisms on the occurrence of leishmaniasis: a systematic review and meta-analysis.

Vital, W., Santos, F., Gonçalves, M., Wyrepkowski, C., Ramasawmy, R., Furtado, S.
21-03-2022
An Bras Dermatol
https://pubmed.ncbi.nlm.nih.gov/35331599

Leishmaniasis is caused by an intracellular protozoan of the Leishmania genus. Mannose-binding lectin (MBL) is a serum complement protein and recognizes lipoprotein antigens in protozoa and the bacterial plasma membrane. Nucleotide variants in the promoter region and exon 1 of the MBL gene can influence its expression or change its molecular structure. To evaluate, through a systematic review, case-control studies of the genetic association of variants in the MBL2 gene and the risk of developing leishmaniasis. This review carried out a search in PubMed, Science Direct, Cochrane Library, Scopus and Lilacs databases for case-control publications with six polymorphisms in the mannose-binding Lectin gene. The following strategy was used: P = Patients at risk of leishmaniasis; I = Presence of polymorphisms; C = Absence of polymorphisms; O = Occurrence of leishmaniasis. Four case/control studies consisting of 791 patients with leishmaniasis and 967 healthy subjects (Control) are included in this meta-analysis. The association of variants in the mannose-binding Lectin gene and leishmaniasis under the allelic genetic model, -550 (Hvs. L), -221 (X vs. Y), +4 (Q vs. P), CD52 (A vs. D), CD54 (A vs. B), CD57 (A vs. C) and A/O genotype (A vs. O) was evaluated. International Prospective Register of Systematic Reviews (PROSPERO): CRD42020201755. The meta-analysis results for any allelic genetic model showed no significant association for the variants within the promoter, the untranslated region, and exon 1, as well as for the wild-type A allele and mutant allele O with leishmaniasis. Caution should be exercised when interpreting these results, as they are based on a few studies, which show divergent results when analyzed separately. This meta-analysis showed a non-significant association between the rs11003125, rs7096206, rs7095891, rs5030737, rs1800450, and rs1800451 polymorphisms of the Mannose-binding Lectin gene and leishmaniasis in any allelic and heterogeneous evaluation.

Granulomatous lesions of the skin: Do not fall into the trap.

Hoornaert, E., Marot, L., Yildiz, H.
21-03-2022
Eur J Intern Med
https://pubmed.ncbi.nlm.nih.gov/35331595

Comparison of immunohistochemical and qPCR methods from granulomatous dermatitis lesions for detection of leishmania in dogs living in endemic areas: a preliminary study.

Porcellato, I., Morganti, G., Antognoni, M., Walczak, K., De Arcangeli, S., Furlanello, T., Quattrone, C., Veronesi, F., Brachelente, C.
24-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05218-6

In canine leishmaniosis (CanL) endemic areas, pathologists often receive skin biopsies for testing with histopathologic findings suggestive-but not conclusive for a definitive diagnosis-of CanL lesions. I the absence of data on the infective status of animals, the diagnosis can therefore be challenging. The aim of this retrospective study was to evaluate the ability of immunohistochemistry (IHC) and quantitative PCR (qPCR) methods to detect Leishmania infection in skin biopsies with a histopathologic diagnosis of lymphoplasmacytic/histiocytic and/or granulomatous dermatitis and to correlate the pattern, depth and severity of the histopathologic lesions with the parasite load detected by

qPCR and IHC. Thirty formalin-fixed, paraffin-embedded skin samples were evaluated by hematoxylin-eosin (H&E) staining, IHC, conventional PCR (cPCR) and qPCR. The severity, pattern and depth of the dermal inflammation and parasite load were graded. Leishmania was detected by H&E staining in 8/30 sections (26.66%) and by IHC in 14/30 samples (46.66%). Parasite DNA was detected in 14/30 samples (46.66%) by cPCR and in 21/30 samples (70%) by qPCR, with an extremely variable parasite load (1.32-62.700 copies). The level of agreement was fair between H&E staining and cPCR (κ=0.32), and moderate between H&E staining and IHC (κ=0.58). The level of agreement between IHC and cPCR was good (κ=0.65); between IHC and qPCR, moderate (κ=0.41); and between cPCR and qPCR, fair (κ=0.28). A significant association was found between the severity of dermal inflammation and the parasitic skin load by IHC, although with weak linear correlation. Our study underlines the difficulty of obtaining a definitive diagnosis of CanL cutaneous lesions, even with the most accurate diagnostic tests currently available. Based on our results, no single test is suitable on its own for the diagnosis of cutaneous lesions caused by Leishmania. However, in the presence of a moderate/severe lymphoplasmacytic/histiocytic and/or granulomatous dermatitis, we suggest performing IHC, as in our study this technique proved to be the method with the highest discriminatory power to estimate the role of the parasite in skin lesions. In mild lesions, IHC loses its discriminatory power and should be effectively combined with techniques such as qPCR.

miRNA-21 regulates CD69 and IL-10 expression in canine leishmaniasis.

Bragato, J., Rebech, G., Freitas, J., Santos, M., Costa, S., Eugênio, F., Santos, P., de Lima, V.
24-03-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265192

Visceral leishmaniasis in humans is a chronic and fatal disease if left untreated. Canine leishmaniasis (CanL) is a severe public health problem because infected animals are powerful transmitters of the parasite to humans via phlebotomine vectors. Therefore, dogs are an essential target for control measures. Progression of canine infection is accompanied by failure of cellular immunity with reduction of circulating lymphocytes and increased cytokines that suppress macrophage function. Studies showed that the regulation of the effector function of macrophages and T cells appears to depend on miRNAs; miRNA-21 (miR-21) shows increased expression in splenic leukocytes of dogs with CanL and targets genes related to the immune response. Mimics and inhibitors of miR-21 were used in vitro to transfect splenic leukocytes from dogs with CanL. After transfection, expression levels of the proteins FAS, FASL, CD69, CCR7, TNF-α, IL-17, IFN-γ, and IL-10 were measured. FAS, FASL, CD69, and CCR7 expression levels decreased in splenic leukocytes from dogs with CanL. The miR-21 mimic decreased CD69 expression in splenic leukocytes from CanL and healthy groups. The miR-21 inhibitor decreased IL-10 levels in culture supernatants from splenic leukocytes in the CanL group. These findings suggest that miR-21 alters the immune response in CanL; therefore, miR-21 could be used as a possible therapeutic target for CanL.

Sand Flies (Diptera: Psychodidae): Fauna and Ecology in the Northeast of Algeria.

Amira, A., Bounamous, A., Kouba, Y., Kadjoudj, N., Zeroual, S., Boubendir, A., Boularouk, Y.
23-03-2022
J Med Entomol
https://pubmed.ncbi.nlm.nih.gov/35323959

Sand flies (Diptera: Psychodidae) transmit several Leishmania (Kinetoplastida: Trypanosomatidae) species, which cause leishmaniasis, a significant public health concern in Algeria. We compared sand fly species abundance and composition among different biotopes (urban, peri-urban, rural areas), bioclimatic zones (humid, sub-humid, semi-arid), and elevation ranges. We also used the additive partitioning of beta diversity to test whether the variation in sand fly composition among biotopes, bioclimatic zones, and elevation ranges is due to species turnover or community subsetting. In total, 7,478 specimens were captured; of which, 7,162 (51.5% males vs. 48.5% females) belong to eight species: Phlebotomus perniciosus Newstead, 1911 (77.4% of the total captured specimens), Phlebotomus perfiliewi Parrot, 1930 (14.6%), Phlebotomus longicuspis Nitzulescu, 1911 (5.9%), Phlebotomus papatasi Scopoli, 1786 (<1%), Phlebotomus sergenti Parrot, 1917 (<1%) and Phlebotomus chadlii Rioux, Juminer et Gibily 1966 (<1%), Sergentomyia minuta Adler et Theodor, 1927 (1%), and Sergentomyia fallax Parrot, 1921 (<1%). Sand fly total abundance showed negative correlations with altitude and was significantly higher in rural areas. Sandfly community composition was significantly different between rural and urban/peri-urban areas. The additive partitioning of beta diversity showed that 71.4% of the compositional dissimilarity among elevation ranges and bioclimates was due to sand fly species turnover, and 28.6% resulted from nestedness. However, the variation in sand fly composition among different biotopes was mainly due to community nestedness. Findings from this study help define the risk of Leishmania transmission and develop methods for vector control in Mila province and Algeria as a whole.

Antileishmanial metallodrugs and the elucidation of new drug targets linked to post-translational modifications machinery: pitfalls and progress.

Monte Neto, R., Moreira, P., de Sousa, A., Garcia, M., Maran, S., Moretti, N.
23-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35320824

Despite the increasing number of manuscripts describing potential alternative antileishmanial compounds, little is

advancing on translating these knowledges to new products to treat leishmaniasis. This is in part due to the lack of standardisations during pre-clinical drug discovery stage and also depends on the alignment of goals among universities/research centers, government and pharmaceutical industry. Inspired or not by drug repurposing, metal-based antileishmanial drugs represent a class that deserves more attention on its use for leishmaniasis chemotherapy. Together with new chemical entities, progresses have been made on the knowledge of parasite-specific drug targets specially after using CRISPR/Cas system for functional studies. In this regard, Leishmania parasites undergoe post-translational modification as key regulators in several cellular processes, which represents an entire new field for drug target elucidation, once this is poorly explored. This perspective review describes the advances on antileishmanial metallodrugs and the elucidation of drug targets based on post-translational modifications, highlighting the limitations on the drug discovery/development process and suggesting standardisations focused on products addressed to who need it most.

Retraction Note: Nucleic acid sensing activates the innate cytosolic surveillance pathway and promotes parasite survival in visceral leishmaniasis.

Das, S., Kumar, A., Mandal, A., Abhishek, K., Verma, S., Kumar, A., Das, P.
22-03-2022
Sci Rep
https://doi.org/10.1038/s41598-022-09098-9

Profilin is involved in G1 to S phase progression and mitotic spindle orientation during Leishmania donovani cell division cycle.

Ambaru, B., Gangadharan, G., Subramanya, H., Gupta, C.
22-03-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265692

Profilin is a multi-ligand binding protein, which is a key regulator of actin dynamics and involved in regulating several cellular functions. It is present in all eukaryotes, including trypanosomatids such as Leishmania. However, not much is known about its functions in these organisms. Our earlier studies have shown that Leishmania parasites express a single homologue of profilin (LdPfn) that binds actin, phosphoinositides and poly- L- proline motives, and depletion of its intracellular pool to 50%of normal levels affects the cell growth and intracellular trafficking. Here, we show, employing affinity pull-down and mass spectroscopy, that LdPfn interacted with a large number of proteins, including those involved in mRNA processing and protein translation initiation, such as eIF4A1. Further, we reveal, using mRNA Seq analysis, that depletion of LdPfn in Leishmania cells (LdPfn+/-) resulted in significantly reduced expression of genes which encode proteins involved in cell cycle regulation, mRNA translation initiation, nucleosides and amino acids transport. In addition, we show that in LdPfn+/- cells, cellular levels of eIF4A1 protein were significantly decreased, and during their cell division cycle, G1-to-S phase progression was delayed and orientation of mitotic spindle altered. These changes were, however, reversed to normal by episomal expression of GFP-LdPfn in LdPfn+/- cells. Taken together, our results indicate that profilin is involved in regulation of G1-to-S phase progression and mitotic spindle orientation in Leishmania cell cycle, perhaps through its interaction with eIF4A1 protein.

Effect of Nanofat Transfer on Leishmaniasis Scars.

Namazi, M., Khosravi, Y., Ketabi, Y.
22-03-2022
Dermatol Surg
https://doi.org/10.1097/DSS.0000000000003390

Punch in the gut: Parasite tolerance of phytochemicals reflects host diet.

Palmer-Young, E., Schwarz, R., Chen, Y., Evans, J.
22-03-2022
Environ Microbiol
https://doi.org/10.1111/1462-2920.15981

Gut parasites of plant-eating insects are exposed to antimicrobial phytochemicals that can reduce infection. Trypanosomatid gut parasites infect insects of diverse nutritional ecologies as well as mammals and plants, raising the question of how host diet-associated phytochemicals shape parasite evolution and host specificity. To test the hypothesis that phytochemical tolerance of trypanosomatids reflects the chemical ecology of their hosts, we compared related parasites from honey bees and mosquitoes-hosts that differ in phytochemical consumption-and contrasted our results with previous studies on phylogenetically related, human-parasitic Leishmania. We identified one bacterial and ten plant-derived substances with known antileishmanial activity that also inhibited honey bee parasites associated with colony collapse. Bee parasites exhibited greater tolerance of chrysin-a flavonoid found in nectar, pollen, and plant resin-derived propolis. In contrast, mosquito parasites were more tolerant of cinnamic acid-a product of lignin decomposition present in woody debris-rich larval habitats. Parasites from both hosts tolerated many compounds that inhibit Leishmania, hinting at possible trade-offs between phytochemical tolerance and mammalian infection. Our results implicate the phytochemistry of host diets as a potential driver of insect-trypanosomatid associations, and identify compounds that could be incorporated into colony diets or floral landscapes to ameliorate infection in bees.

Semisynthetic triterpenes led to the generation of selective antitrypanosomal lead compounds.

Guilhon-Simplicio, F., Serrão, C., Pinto, A., Pacheco, P., Faria, R., da Rocha, D., Ferreira, V., Pereira-Junior, R., Matheeussen, A., Baán, A., Kiekens, F., de Meneses Pereira, M., Lima, E., Winter, H., Cos, P.
21-03-2022
Chem Biol Drug Des
https://doi.org/10.1111/cbdd.14040

Triterpenes α,β-amyrin are naturally occurring molecules that can serve as building blocks for synthesizing new chemical entities. This study synthesized acyl, carboxyesther, NSAID, and nitrogenous derivatives and evaluated their antimicrobial activity. A cyclodextrin complexation method was developed to improve the solubility of the derivatives. Of the 17 derivatives tested, five exhibited activity against Trypanosoma cruzi, T. brucei, Leishmania infantum, Candida albicans, Staphylococcus aureus, and Escherichia coli. The 9a/9b mixture showed weak activity against the parasites (IC_{50} 24.45-40.32 µM). However, it showed no activity for the other microorganisms. Derivatives 14a/14b exhibited potent activity against T. cruzi (IC_{50} 2.0 nM) in this tested concentration did not show activity to the other microorganisms and were not cytotoxic. Derivatives 15a/15b and 16a/16b demonstrated relevant activity against the parasites (IC_{50} 2.24-5.44 µM), but were also cytotoxic. Derivatives 17a/17b showed low activity against the tested parasites (IC_{50} 21.70-22.79 µM), but they were selective since they did not show activity against other microorganisms. In docking studies, in general, all derivatives showed complementarity with the CYP51 binding site of the trypanosomatid mainly by hydrophobic interactions; thus, it is not conclusive that the molecules act by inhibiting this enzyme. Our results showed that triterpenes derivatives with antitrypanosomal activity could be synthesized by an inexpensive and rapid method.

Cysticercose

Dracunculose

Echinococcose

Species and genotypes belonging to Echinococcus granulosus sensu lato complex causing human cystic echinococcosis in Europe (2000-2021): a systematic review.

Casulli, A., Massolo, A., Saarma, U., Umhang, G., Santolamazza, F., Santoro, A.
28-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05197-8

This study aimed to fill a gap of knowledge by providing a quantitative measure of molecularly identified species and genotypes belonging to Echinococcus granulosus sensu lato (s.l.) causing human cystic echinococcosis (CE) in Europe during the period 2000-2021. As these species and genotypes are characterized by genetic, animal host and geographical differences, studying the E. granulosus s.l. complex is epidemiologically relevant. A systematic review (SR) was conducted on the basis of both scientific and grey literature considering primary studies between 2000 and 2021 in four databases. From a total of 1643 scientific papers, 51 records were included in the SR. The main inclusion criterion for this study was the molecular confirmation of E. granulosus s.l. at the genotype/species level as a causative agent of human CE cases in selected European countries. Relevant data were obtained from 29 out of 39 eligible European countries. This SR identified 599 human molecularly confirmed echinococcal cysts: 460 (76.8%) identified as E. granulosus sensu stricto (s.s.), 130 (21.7%) as E. canadensis cluster (G6/7 and G10), 7 (1.2%) as E. ortleppi (G5), and 2 as E. vogeli (0.3%). Three geographical hotspots of human CE caused by different species of the E. granulosus s.l. complex were identified: (1) E. granulosus s.s. in Southern and South-eastern Europe (European-Mediterranean and Balkan countries); (2) E. canadensis (G6/7) in Central and Eastern Europe; (3) E. ortleppi in Central and Western Europe. This SR also identified data gaps that prevented a better definition of the geographical distribution of the Echinococcus granulosus s.l. species complex in Europe: western Balkan countries, part of Central Europe, and Baltic countries. These results mandate longitudinal, multi-centre, intersectoral and transdisciplinary studies which consider both molecular and clinical epidemiology in animals and humans. Such studies would be valuable for a better understanding of the transmission of the E. granulosus s.l. species complex and their potential clinical impact on humans.

Trematodoses d'origine alimentaire (clonorchiase, opisthorchiase, fasciolase et paragonimose)

Origins, phylogenetic relationships and host-parasite interactions of Troglotrematoidea since the cretaceous.

Vainutis, K., Voronova, A., Duscher, G., Shchelkanov, E., Shchelkanov, M.
22-03-2022
Infect Genet Evol
https://pubmed.ncbi.nlm.nih.gov/35337967

In the current study, we raise the issue concerning origins and historical relationships of the trematodes from the families Troglotrematidae and Paragonimidae using phylogenetic analysis and molecular-clock method for estimating evolutionary rates. For the first time we provided 28S rRNA gene fragment (1764 bp) for the type species Troglotrema acutum - zoonotic trematodes that cause cranial lesions (troglotremiasis) in mustelid and canid mammals of the Central Europe, Iberian Peninsula, and North-West Caucasus. Molecular genetic analysis revealed that T. acutum belongs to the monophyletic family Troglotrematidae sister with the family Paragonimidae. The family Troglotrematidae includes five genera: Nanophyetus, Troglotrema, Skrjabinophyetus, Nephrotrema, and Macroorchis; and the family Paragonimidae is monotypic including the only genus Paragonimus. We recover the superfamily Troglotrematoidea for these two families. Divergence of the common ancestor of the superfamily Troglotrematoidea (common troglotrematoid ancestor) likely occurred during the Cretaceous period of the Mesozoic Era and potentially originated in the Asiatic region. The lineage of the family Troglotrematidae is much closer to the common troglotrematoid ancestor than the species of the family Paragonimidae. The radiation time of the common troglotrematoid ancestor (126 Ma, the Early Cretaceous), and formation of the families Troglotrematidae and Paragonimidae (96 Ma and 73 Ma respectively, the Late Cretaceous) corresponds to the time of settling in East Asia by many species of mammaliaforms (about 130-70 Ma).

Field evaluation of the enhanced MM3-COPRO ELISA test for the diagnosis of Fasciola hepatica infection in sheep.

Mezo, M., González-Warleta, M., Castro-Hermida, J., Martínez-Sernández, V., Ubeira, F.
24-03-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265569

Fasciolosis is a severe zoonosis responsible for major economic losses in livestock. The enhanced MM3-COPRO test (eMM3-COPRO) and the commercial version BIO K 201 (Bio-X Diagnostics, Rochefort, Belgium) are widely used as immunodiagnostic tools for the specific detection of coproantigens released by Fasciola during the late prepatent and patent stages of infection. However, performance of the eMM3-COPRO has never been evaluated under field conditions. To address this gap, a large number of ovine faecal samples, collected in a region where fasciolosis is endemic (Galicia, NW Spain), were analyzed. Two groups of sheep flocks were selected according to the Fasciola infection status: 'Fasciola-free' and 'Fasciola-infected' flocks. 'Fasciola-free' flocks were seronegative flocks with no history of fasciolosis detected by either coproscopy or necropsy in the last 5 years. Faecal samples from these sheep were used to calculate a cut-off value for infection (OD = 0.021). The cut-off was calculated using a bootstrap resampling method that enables estimation of the sampling distribution of the statistical parameters without making assumptions about the underlying data distribution. 'Fasciola-infected' flocks were characterized by high seroprevalence, a history of fasciolosis and periodical treatment with flukicides. Samples from these flocks were used to estimate the diagnostic accuracy of the eMM3-COPRO relative to coproscopy, which although limited by poor sensitivity is the only reference test available for diagnosing fasciolosis in vivo. To overcome this limitation, all animals classified positive by eMM3-COPRO were treated with triclabendazole and then retested. The eMM3-COPRO displayed higher sensitivity than coproscopy, as it detected coproantigens in all samples with positive coproscopy and in 12% of samples with negative coproscopy. The test also proved highly specific as coproantigens disappeared after the treatment. The eMM3-COPRO was less time consuming than coproscopy, particularly when the procedure involved numerous samples, and showed promise as a tool for monitoring flukicide efficacy.

Transcriptomic landscape of hepatic lymph nodes, peripheral blood lymphocytes and spleen of swamp buffaloes infected with the tropical liver fluke Fasciola gigantica.

Hu, R., Zhang, F., Ma, Q., Ehsan, M., Zhao, Q., Zhu, X.
23-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010286

The tropical liver fluke Fasciola gigantica is a parasitic helminth that has been frequently reported to infect mammals, typically involving water buffaloes. In this study, we characterized the tissue transcriptional landscape of buffaloes following infection by F. gigantica. RNAs were isolated from hepatic lymph nodes (hLNs), peripheral blood lymphocytes (pBLs), and spleen at 3-, 42- and 70-days post-infection (dpi), and all samples were subjected to RNA sequencing analyses. At 3 dpi, 2603, 460, and 162 differentially expressed transcripts (DETs) were detected in hLNs, pBLs, and spleen, respectively. At 42 dpi, 322, 937, and 196 DETs were detected in hLNs, pBLs, and spleen, respectively. At 70 dpi, 376, 334, and 165 DETs were detected in hLNs, pBLs, and spleen, respectively. Functional enrichment analysis identified upregulated immune-related pathways in the infected tissues involved in innate and adaptive immune responses, especially in hLNs at 42 and 70 dpi, and pBLs at 3 and 42 dpi. The upregulated transcripts in spleen were not enriched in any immune-related pathway. Co-expression network analysis further identified transcriptional changes associated with immune response to F. gigantica infection. Receiver operating characteristic (ROC) curve analysis showed that 107 genes in hLNs, 32 genes in pBLs, and 36 genes in spleen correlated with F. gigantica load. These findings provide new insight into molecular mechanisms and signaling pathways associated with F. gigantica infection in buffaloes.

Molecular characterization of a novel GSTO2 of Fasciola hepatica and its roles in modulating murine macrophages.

Wang, X., Zhao, C., Zhang, G., Zhang, K., Li, Z., Shang, Y., Ning, C., Ji, C., Xia, X., Cai, X., Qiao, J., Meng, Q.
22-03-2022
Parasite
https://doi.org/10.1051/parasite/2022016

Fascioliasis is an important zoonotic helminthic disease caused by Fasciola hepatica and poses a serious threat to global public health. To evade the immune response of its host (humans or animals), F. hepatica secretes various antioxidant enzymes such as glutathione transferase (GST) to facilitate its invasion, migration and parasitism in vivo. To investigate the biological functions of a novel omega-class GST (GSTO), the molecular features of GSTO2 of F. hepatica were analyzed by online software, and the biochemical properties in vitro of recombinant GSTO2 (rGSTO2) were dissected. Then, the regulatory roles of rGSTO2 protein in murine macrophages in vitro were further explored. The results revealed that the GSTO2 gene encodes 254 amino acids, which harbor the characteristic N-terminal domain (βαβαββα) and C-terminal domain (α-helical) of the cytoplasmic GST superfamily. GSTO2 was mainly expressed in F. hepatica vitelline follicles, intestinal tract, excretory pores and vitelline cells, with thioltransferase and dehydroascorbate reductase activities. Moreover, rGSTO2 protein could be taken up by murine macrophages and significantly inhibit the viability of macrophages. In addition, rGSTO2 protein could significantly promote apoptosis and modulate the expression of cytokines in macrophages. These findings suggested that F. hepatica GSTO2 plays an important role in modulating the physiological functions of macrophages, whereby this protein might be involved in immunomodulatory and anti-inflammatory roles during infection. This study provided new insights into the immune-evasion mechanism of F. hepatica and may contribute to the development of a potential anti-inflammatory agent.

FILARIOSE LYMPHATIQUE

Prevention of bacterial complications of scabies using mass drug administration: A population-based, before-after trial in Fiji, 2018-2020.

Thean, L., Romani, L., Engelman, D., Wand, H., Jenney, A., Mani, J., Paka, J., Cua, T., Taole, S., Silai, M., Ashwini, K., Sahukhan, A., Kama, M., Tuicakau, M., Kado, J., Parnaby, M., Carvalho, N., Whitfeld, M., Kaldor, J., Steer, A.
22-03-2022
Lancet Reg Health West Pac
https://doi.org/10.1016/j.lanwpc.2022.100433

Scabies is an important predisposing factor of impetigo which can lead to serious bacterial complications. Ivermectin-based mass drug administration can substantially reduce scabies and impetigo prevalence in endemic settings, but the impact on serious bacterial complications is not known. We conducted a before-after trial in the Northern Division of Fiji (population: 131,914) of mass drug administration for scabies control. Prospective surveillance was conducted from 2018 to 2020. Mass drug administration took place in 2019, involving two doses of oral ivermectin or topical permethrin, delivered alongside diethylcarbamazine and albendazole for lymphatic filariasis. The primary outcomes were incidence of hospitalisations with skin and soft tissue infections, and childhood invasive infections and post-streptococcal sequelae. Secondary outcomes included presentations to primary healthcare with skin infections and community prevalence of scabies and impetigo. The incidence of hospitalisations with skin and soft tissue infections was 17% lower after the intervention compared to baseline (388 vs 467 per 100,000 person-years; incidence rate ratio 0.83, 95% CI, 0.74 to 0.94; $P = 0.002$). There was no difference in incidence of childhood invasive infections and post-streptococcal sequelae. Incidence of primary healthcare presentations with scabies and skin infections was 21% lower (89.2 vs 108 per 1000 person-years, incidence rate ratio, IRR 0.79, 95% CI, 0.78 to 0.82). Crude community prevalence of scabies declined from 14.2% to 7.7% (cluster-adjusted prevalence 12.5% to 8.9%; prevalence ratio 0.71, 95% CI, 0.28 to 1.17). Cluster-adjusted prevalence of impetigo declined from 15.3% to 6.1% (prevalence ratio 0.4, 95% CI, 0.18 to 0.86). Mass drug administration for scabies control was associated with a substantial reduction in hospitalisations for skin and soft tissue infections. National Health and Medical Research Council of Australia and Scobie and Claire Mackinnon Trust.

Lymphatic filariasis in 2016 in American Samoa: Identifying clustering and hotspots using non-spatial and three spatial analytical methods.

Wangdi, K., Sheel, M., Fuimaono, S., Graves, P., Lau, C.
28-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010262

American Samoa completed seven rounds of mass drug administration from 2000-2006 as part of the Global Programme to Eliminate Lymphatic Filariasis (LF). However, resurgence was confirmed in 2016 through WHO-recommended school-based transmission assessment survey and a community-based survey. This paper uses data from the 2016 community survey to compare different spatial and non-spatial methods to characterise clustering and hotspots of LF. Non-spatial clustering of infection markers (antigen [Ag], microfilaraemia [Mf], and antibodies (Ab [Wb123, Bm14, Bm33]) was assessed using intra-cluster correlation coefficients (ICC) at household and village levels. Spatial dependence, clustering and hotspots were examined using semivariograms, Kulldorf's scan statistic and Getis-Ord Gi* statistics based on locations of surveyed households. The survey included 2671 persons (750 households, 730 unique locations in 30 villages). ICCs were higher at household (0.20-0.69) than village levels (0.10-0.30) for all infection markers.

Semivariograms identified significant spatial dependency for all markers (range 207-562 metres). Using Kuldorff's scan statistic, significant spatial clustering was observed in two previously known locations of ongoing transmission: for all markers in Fagali'i and all Abs in Vaitogi. Getis-Ord Gi* statistic identified hotspots of all markers in Fagali'i, Vaitogi, and Pago Pago-Anua areas. A hotspot of Ag and Wb123 Ab was identified around the villages of Nua-Seetaga-Afao. Bm14 and Bm33 Ab hotspots were seen in Maleimi and Vaitogi-Ili'ili-Tafuna. Our study demonstrated the utility of different non-spatial and spatial methods for investigating clustering and hotspots, the benefits of using multiple infection markers, and the value of triangulating results between methods.

Crude protein fraction with high thioredoxin reductase (TrxR) enzyme activity from filarial parasite Setaria cervi counters lipopolysaccharide (LPS)-induced inflammation in macrophages.

Joardar, N., Jana, K., Babu, S.
23-03-2022
Parasitol Res
https://doi.org/10.1007/s00436-022-07495-7

Host-parasite interaction has always been an area of interest to the parasite biologists. The complex immune interactions between the parasite and/or the parasite-derived products with the host immune cells determine the fate of the disease biology. Parasitic organisms are widely equipped with a vast array of protective machineries including antioxidant enzymes to withstand the hostile condition inside the host body. The reactive oxygen species (ROS) generated inside the host as a result of parasitic intervention can be endured by the parasite by their own tools to ensure their survival. One such antioxidant enzyme in the filarial parasite that plays a significant role in redox homeostasis, survivability and disease progression is the thioredoxin reductase (TrxR). Herein, we have projected a crude lysate of the bovine filarial parasite Setaria cervi enriched with high TrxR enzyme activity has the capacity to downregulate lipopolysaccharide (LPS)-induced inflammatory macrophages. TrxR-mediated inhibition of the TLR4-NF-κB axis resulting into downregulation of the pro-inflammatory cytokines with concomitant upregulation of the anti-inflammatory cytokines supports the filarial parasite to produce an anti-inflammatory milieu which ultimately promotes worm survivability inside the host and pathogenesis.

MYCETOME

ONCHOCERCOSE

Pharmacokinetics of oral moxidectin in individuals with Onchocerca volvulus infection.

Tan, B., Opoku, N., Attah, S., Awadzi, K., Kuesel, A., Lazdins-Helds, J., Rayner, C., Ryg-Cornejo, V., Sullivan, M., Fleckenstein, L.
25-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010005

Onchocerciasis ("river blindness"), is a neglected tropical disease caused by the filarial nematode Onchocerca volvulus and transmitted to humans through repeated bites by infective blackflies of the genus Simulium. Moxidectin was approved by the United States Food and Drug Administration in 2018 for the treatment of onchocerciasis in people at least 12 years of age. The pharmacokinetics of orally administered moxidectin in 18- to 60-year-old men and women infected with Onchocerca volvulus were investigated in a single-center, ivermectin-controlled, double-blind, randomized, single-ascending-dose, ascending severity of infection study in Ghana. Participants were randomized to either a single dose of 2, 4 or 8 mg moxidectin or ivermectin. Pharmacokinetic samples were collected prior to dosing and at intervals up to 12 months post-dose from 33 and 34 individuals treated with 2 and 4 mg moxidectin, respectively and up to 18 months post-dose from 31 individuals treated with 8 mg moxidectin. Moxidectin plasma concentrations were determined using high-performance liquid chromatography with fluorescence detection. Moxidectin plasma AUC0-∞ (2 mg: 26.7-31.7 days*ng/mL, 4 mg: 39.1-60.0 days*ng/mL, 8 mg: 99.5-129.0 days*ng/mL) and Cmax (2mg, 16.2 to17.3 ng/mL, 4 mg: 33.4 to 35.0 ng/mL, 8 mg: 55.7 to 74.4 ng/mL) were dose-proportional and independent of severity of infection. Maximum plasma concentrations were achieved 3 to 4 hours after drug administration. The mean terminal half-lives of moxidectin were 20.6, 17.7, and 23.3 days at the 2, 4 and 8 mg dose levels, respectively. We found no relationship between severity of infection (mild, moderate or severe) and exposure parameters (AUC0-∞ and Cmax), T1/2 and Tmax for moxidectin. Tmax, volume of distribution (V/F) and oral clearance (CL/F) are similar to those in healthy volunteers from Europe. From a pharmacokinetic perspective, moxidectin is an attractive long-acting therapeutic option for the treatment of human onchocerciasis.

Epileptogenesis in Common Parasitic Infections.

Revue de littérature

Mazumder, R., Lee, J.
25-03-2022
Curr Neurol Neurosci Rep
https://doi.org/10.1007/s11910-022-01187-6

Neurocysticercosis (NCC) has been well recognized as a leading cause of epilepsy. More recently, studies of other parasitic diseases such as cerebral malaria (CM)

and onchocerciasis are yielding novel insights into the pathogenesis of parasite-associated epilepsy. We compare the clinical and electrophysiological findings in epilepsy associated with these highly prevalent parasites and discuss the mechanisms involved in epileptogenesis. Electrophysiological and imaging biomarkers continue to emerge, and individuals who are at-risk of developing parasite-associated epilepsies are being identified with greater reliability. While both Taenia solium and Plasmodium falciparum directly affect the brain parenchyma, Onchocerca volvulus is not known to invade the central nervous system. Thus, the causal association between O. volvulus and epilepsy remains controversial. Both NCC and CM have a well-defined acute phase when the parasites directly or indirectly invade the brain parenchyma and lead to local inflammatory changes. This is followed by a chronic phase marked by recurrent seizures. However, these stages of epileptogenic process have not been identified in the case of O. volvulus.

SCHISTOSOMIASE

Alterations in blood glucose concentration in wild rodents, Holochilus sciureus, naturally infected with Schistosoma mansoni.

Rodrigues, J., Lira, M., Nogueira, R., Gomes, G., Licá, I., Silva, J., Miranda, G., Silva-Souza, N.
28-03-2022
Rev Bras Parasitol Vet
https://pubmed.ncbi.nlm.nih.gov/35352759

The present study aimed to evaluate the changes in peripheral blood glucose concentrations induced by Schistosoma mansoni infection in Holochilus sciureus rodents, a wild reservoir of the parasite. Glucose concentration was measured in the plasma of blood samples using a colorimetric enzymatic test. Biological parameters and S. mansoni burden in each rodent were also verified and correlated with glucose concentrations. A total of 76 H. sciureus were captured, out of which 20 (26%) were infected with S. mansoni (n=13 males and n=7 females). Although the parasite burden was comparable between the sexes, blood glucose concentration was lower in infected males and almost unchanged in females. Furthermore, histopathological data revealed that male rodents had a greater hepatic granulomatous inflammatory reaction than females. In addition, we also confirmed that the weight and total length of the analyzed animals had no effect on glucose levels. Therefore, natural infection with S. mansoni in H. sciureus may have a lower impact on glycemic homeostasis in females, which will help us understand the role of these rodents as reservoirs of S. mansoni.

Host Liver-Derived Extracellular Vesicles Deliver miR-142a-3p Induces Neutrophil Extracellular Traps via Targeting WASL to Block the Development of Schistosoma japonicum.

Wang, L., Zhu, Z., Liao, Y., Zhang, L., Yu, Z., Yang, R., Wu, J., Wu, Z., Sun, X.
26-03-2022
Mol Ther
https://pubmed.ncbi.nlm.nih.gov/35351657

Schistosomiasis is an important neglected tropical disease. Interactions between the host immune system and schistosomes are complex. Neutrophils contribute to clearance of large pathogens primarily by releasing neutrophil extracellular traps (NETs). However, the functional role of NETs in clearing schistosomes remains unclear. Herein, we report that extracellular vesicles (EVs) derived from the liver of Schistosoma japonicum (S. japonicum)-infected mice (IL-EVs) induce NETs release by delivering miR-142a-3p to target WASL and block the development of S. japonicum. WASL knockout accelerated the formation of NETs that blocked further development of S. japonicum. miR-142a-3p and NETs up-regulated the expression of CCL2, which recruits macrophages that block S. japonicum development. However, S. japonicum inhibited NETs formation in wild-type mice by up-regulating host interleukin (IL)-10 expression. In contrast, in WASL-knockout mice, IL-10 expression was down-regulated, and S. japonicum-mediated inhibition of NETs formation was significantly reduced. IL-EV-mediated induction of NETs formation is thus an anti-schistosome response that can be counteracted by S. japonicum. These findings suggest that IL-EV-mediated induction of NETs formation plays a key role in schistosomes infection and that WASL is a potential therapeutic target in schistosomiasis and other infectious diseases.

Kidney complications of parasitic diseases.

Revue de littérature

Daher, E., da Silva Junior, G., Trivedi, M., Fayad, T., Srisawat, N., Nair, S., Siriyasatien, P., de Lacerda, M., Baptista, M., Vankalakunti, M., Jha, V.
28-03-2022
Nat Rev Nephrol
https://doi.org/10.1038/s41581-022-00558-z

Parasitic agents have been known to cause human disease since ancient times and are endemic in tropical and subtropical regions. Complications of parasitic diseases, including kidney involvement, are associated with worse outcomes. Chagas disease, filariasis, leishmaniasis, malaria and schistosomiasis are important parasitic diseases that can damage the kidney. These diseases affect millions of people worldwide, primarily in Africa, Asia and Latin America, and kidney involvement is associated with increased mortality. The most common kidney complications of parasitic diseases are acute kidney injury, glomerulonephritis and tubular dysfunction. The mechanisms that underlie parasitic disease-associated kidney injury include direct parasite damage;

immunological phenomena, including immune complex deposition and inflammation; and systemic manifestations such as haemolysis, haemorrhage and rhabdomyolysis. In addition, use of nephrotoxic drugs to treat parasitic infections is associated with acute kidney injury. Early diagnosis of kidney involvement and adequate management is crucial to prevent progression of kidney disease and optimize patient recovery.

nMolluskicidal activity of 3-aryl-2-hydroxy-1,4-naphthoquinones against Biomphalaria glabrata.

Martins, D., do Amaral E Silva, N., Ferreira, V., Rangel, L., Dos Santos, J., Faria, R.
25-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35346667

Schistosomiasis is the second most prevalent parasitic infectious disease after malaria, which affects millions of people worldwide and causes health and socioeconomic problems. The snail Biomphalaria glabrata is an intermediate host for the helminth, which is the causative agent of schistosomiasis: Schistosoma mansoni. One crucial strategy for controlling the disease is the eradication of the snail host. Niclosamide is the unique molluskicide applied in large-scale control programs, but its selectivity to other species is not adequate. Therefore, there is an urgent need to develop new molluskicides that are inexpensive, safe, and selective. Quinones are ubiquitous, playing important biological roles in fungi, plants, and others. Many synthetic molecules with relevant biological activities that contain the quinone nucleus in their structure are on the market in the therapy of cancer, malaria, or toxoplasmosis, for example. Derivatives of quinones are tools in the development of new molluskicides for Abbott laboratories. In the present work, 3-aryl-2-hydroxy-1,4-naphthoquinones (ANs) were tested for molluskicide activity against Biomphalaria glabrata. The lethal concentration was determined for 48 hours of continuous exposure. The naphthoquinones were found to have molluskicide properties. AN-15 was recorded as the highest mortality. Additionally, this analog exhibited in silico reduced ambient toxicity when compared to niclosamide. The findings of this study demonstrate that 3-aryl-2-hydroxy-1,4-naphthoquinones are effective for the management of Biomphalaria glabrata under laboratory conditions.

Hybridization increases genetic diversity in Schistosoma haematobium populations infecting humans in Cameroon.

Teukeng, F., Blin, M., Bech, N., Gomez, M., Zein-Eddine, R., Simo, A., Allienne, J., Tchuem-Tchuenté, L., Boissier, J.
26-03-2022
Infect Dis Poverty
https://doi.org/10.1186/s40249-022-00958-0

Hybrids between Schistosoma haematobium (Sh) and S. bovis (Sb) have been found in several African countries as well as in Europe. Since the consequences of this hybridization are still unknown, this study aims to verify the presence of such hybrids in Cameroonian humans, to describe the structure of S. haematobium populations on a large geographic scale, and to examine the impact of these hybrids on genetic diversity and structure of these populations. From January to April 2019, urine from infected children was collected in ten geographically distinct populations. Miracidia were collected from eggs in this urine. To detect the presence of hybrids among these miracidia we genotyped both Cox1 (RD-PCR) and ITS2 gene (PCR-RFLP). Population genetic diversity and structure was assessed by genotyping each miracidium with a panel of 14 microsatellite markers. Gene diversity was measured using both heterozygosity and allelic richness indexes, and genetic structure was analyzed using paired Fst, PCA and Bayesian approaches. Of the 1327 miracidia studied, 88.7% were identified as pure genotypes of S. haematobium (Sh_Sh/Sh) while the remaining 11.3% were hybrids (7.0% with Sh_Sh/Sb, 3.7% with Sb_Sb/Sh and 0.4% with Sb_Sh/Sb). No miracidium has been identified as a pure genotype of S. bovis. Allelic richness ranged from 5.55 (Loum population) to 7.73 (Matta-Barrage) and differed significantly between populations. Mean heterozygosity ranged from 53.7% (Loum) to 59% (Matta Barrage) with no significant difference. The overall genetic differentiation inferred either by a principal component analysis or by the Bayesian approach shows a partial structure. Southern populations (Loum and Matta Barrage) were clearly separated from other localities but genetic differentiation between northern localities was limited, certainly due to the geographic proximity between these sites. Hybrids between S. haematobium and S. bovis were identified in 11.3% of miracidia that hatched from eggs present in the urine of Cameroonian schoolchildren. The percentages of these hybrids are correlated with the genetic diversity of the parasite, indicating that hybridization increases genetic diversity in our sampling sites. Hybridization is therefore a major biological process that shapes the genetic diversity of S. haematobium.

Point-of-Care Sample Preparation and Automated Quantitative Detection of Schistosoma haematobium Using Mobile Phone Microscopy.

Armstrong, M., Harris, A., D'Ambrosio, M., Coulibaly, J., Essien-Baidoo, S., Ephraim, R., Andrews, J., Bogoch, I., Fletcher, D.
28-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-1071

Schistosoma haematobium continues to pose a significant public health burden despite ongoing global control efforts. One of several barriers to sustained control (and ultimately elimination) is the lack of access to highly sensitive diagnostic or screening tools that are inexpensive, rapid, and can be used at the point of sample collection. Here, we report an automated point-of-care diagnostic based on mobile phone microscopy that rapidly images and identifies S. haematobium eggs in urine samples. Parasite eggs are filtered from urine within a specialized, inexpensive cartridge that is then automatically imaged by the mobile phone microscope (the

"SchistoScope"). Parasite eggs are captured at a constriction point in the tapered cartridge for easy imaging, and the automated quantification of eggs is obtained upon analysis of the images by an algorithm. We demonstrate S. haematobium egg detection with greater than 90% sensitivity and specificity using this device compared with the field gold standard of conventional filtration and microscopy. With simple sample preparation and image analysis on a mobile phone, the SchistoScope combines the diagnostic performance of conventional microscopy with the analytic performance of an expert technician. This portable device has the potential to provide rapid and quantitative diagnosis of S. haematobium to advance ongoing control efforts.

National mapping of schistosomiasis, soil-transmitted helminthiasis and anaemia in Yemen: Towards better national control and elimination.

Johari, N., Annuzaili, D., El-Talabawy, H., Ba-Break, M., Al-Mekhlafi, A., Al-Eryani, S., Alkohlani, A., Gabrielli, A., Ben-Ismail, R., Alhaidari, S., Muaydh, A., Alshami, R., Al Gunaid, M., Hamed, A., Kamel, N., Palacio, K., Fleming, F., French, M.
25-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010092

Schistosomiasis (SCH) and soil-transmitted helminthiasis (STH) are known to be endemic in Yemen. However, the distribution of both diseases had not previously been assessed by a well-structured national mapping study covering all governorates. The main aim of this study was, therefore, to map the prevalence of SCH and STH in Yemen in order to better inform implementation of effective national control and elimination interventions. The assessment of the distribution of anaemia was also included as a well-known consequence of infection with both SCH and STH. Secondarily, the study aimed to provide a broad indication of the impact of large-scale treatment on the distribution of infection. To achive these aims, 80,432 children (10-14 years old) from 2,664 schools in 332 of Yemen's 333 districts were included, in 2014, into this national cross-sectional survey. Countrywide, 63.3% (210/332) and 75.6% (251/332) of districts were found to be endemic for SCH and STH respectively. More districts were affected by intestinal than urogenital SCH (54.2% and 31.6% respectively). SCH infection was mostly mild and moderate, with no districts reporting high infection. One quarter (24.4%) of Yemeni districts had high or moderate levels of Ascaris lumbricoides infection. Infection with Trichuris trichiura was the second most common STH (44.9% of districts infected) after A. lumbricoides (68.1%). Hookworm was the least prevalent STH (9.0%). Anaemia was prevalent in 96.4% of districts; it represented a severe public health problem (prevalence ≥ 40%) in 26.5% of districts, and a mild to moderate problem in two thirds of the districts (33.7% and 36.1% respectively). This study provided the first comprehensive mapping of SCH, STH, and anaemia across the country. This formed the basis for evaluating and continuing the national control and elimination programme for these neglected tropical diseases in Yemen.

Neutrophils and schistosomiasis: a missing piece in pathology.

Revue de littérature

Sanches, R., Mambelli, F., Oliveira, S.
25-03-2022
Parasite Immunol
https://doi.org/10.1111/pim.12916

Schistosomiasis is a chronic human parasitic disease that causes serious health problems worldwide. The disease-associated liver pathology is one of the hallmarks of infections by S. mansoni and S. japonicum, and is accountable for the debilitating condition found in infected patients. In the past few years, investigative studies have highlighted the key role played by neutrophils and the influence of inflammasome signaling pathway in different pathological conditions. However, it is noteworthy that the study of inflammasome activation in neutrophils has been overlooked by reports concerning macrophages and monocytes. This interplay between neutrophils and inflammasomes is much more poorly investigated during schistosomiasis. Herein we reviewed the role of neutrophils during schistosomiasis and addressed the potential connection between these cells and inflammasome activation in this context.

Construction of cell factory capable of efficiently converting L-tryptophan into 5-hydroxytryptamine.

Wang, Y., Chen, X., Chen, Q., Zhou, N., Wang, X., Zhang, A., Chen, K., Ouyang, P.
24-03-2022
Microb Cell Fact
https://doi.org/10.1186/s12934-022-01745-0

L-Tryptophan (L-Trp) derivatives such as 5-hydroxytryptophan (5-HTP) and 5-hydroxytryptamine (5-HT), N-Acetyl-5-hydroxytryptamine and melatonin are important molecules with pharmaceutical interest. Among, 5-HT is an inhibitory neurotransmitter with proven benefits for treating the symptoms of depression. At present, 5-HT depends on plant extraction and chemical synthesis, which limits its mass production and causes environmental problems. Therefore, it is necessary to develop an efficient, green and sustainable biosynthesis method to produce 5-HT. Here we propose a one-pot production of 5-HT from L-Trp via two enzyme cascades for the first time. First, a chassis cell that can convert L-Trp into 5-HTP was constructed by heterologous expression of tryptophan hydroxylase from Schistosoma mansoni (SmTPH) and an artificial endogenous tetrahydrobiopterin (BH_4) module. Then, dopa decarboxylase from Harminia axyridis (HaDDC), which can specifically catalyse 5-HTP to 5-HT, was used for 5-HT production. The cell factory, E. coli BL21(DE3)ΔtnaA/BH_4/HaDDC-SmTPH, which contains SmTPH and HaDDC, was constructed for 5-HT synthesis. The highest concentration of 5-HT reached 414.5±1.6 mg/L (with conversion rate of 25.9 mol%) at the optimal conditions (substrate concentration,2 g/L; induced temperature, 25℃; IPTG concentration, 0.5 mM; catalysis temperature, 30℃; catalysis time, 72 h). This protocol provided an efficient one-

pot method for converting. L-Trp into 5-HT production, which opens up possibilities for the practical biosynthesis of natural 5-HT at an industrial scale.

Changes in the lipid profile of hamster liver after Schistosoma mansoni infection, characterized by mass spectrometry imaging and LC-MS/MS analysis.

Wiedemann, K., Peter Ventura, A., Gerbig, S., Roderfeld, M., Quack, T., Grevelding, C., Roeb, E., Spengler, B.
23-03-2022
Anal Bioanal Chem
https://doi.org/10.1007/s00216-022-04006-6

Schistosomiasis, caused by the human parasite Schistosoma mansoni, is one of the WHO-listed neglected tropical diseases (NTDs), and it has severe impact on morbidity and mortality, especially in Africa. Not only the adult worms but also their eggs are responsible for health problems. Up to 50% of the eggs produced by the female worms are not excreted with the feces but are trapped in the host tissue, such as the liver, where they provoke immune responses and a change in the lipid profile. We built up a database with 372 infection markers found in livers of S. mansoni-infected hamsters, using LC-MS/MS for identification, followed by statistical analysis. Most of them belong to the lipid classes of phosphatidylcholines (PCs), phosphatidylethanolamines (PEs), and triglycerides (TGs). We assigned some of these markers to specific anatomical structures by applying high-resolution MALDI MSI to cryosections of hamster liver and generating ion images based on the marker list from the LC-MS/MS experiments. Furthermore, enrichment and depletion of several markers were visualized.

Estimating the financial impact of livestock schistosomiasis on traditional subsistence and transhumance farmers keeping cattle, sheep and goats in northern Senegal.

Adeyemo, P., Léger, E., Hollenberg, E., Diouf, N., Sène, M., Webster, J., Häsler, B.
22-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-021-05147-w

Schistosomiasis is a disease that poses major threats to human and animal health, as well as the economy, especially in sub-Saharan Africa (SSA). Whilst many studies have evaluated the economic impact of schistosomiasis in humans, to date only one has been performed in livestock in SSA and none in Senegal. This study aimed to estimate the financial impact of livestock schistosomiasis in selected regions of Senegal. Stochastic partial budget models were developed for traditional ruminant farmers in 12 villages in northern Senegal. The models were parameterised using data from a cross-sectional survey, focus group discussions, scientific literature and available statistics. Two scenarios were defined: scenario 1 modelled a situation in which farmers tested and treated their livestock for schistosomiasis, whilst scenario 2 modelled a situation in which there were no tests or treatment. The model was run with 10,000 iterations for 1 year; results were expressed in West African CFA francs (XOF; 1 XOF was equivalent to 0.0014 GBP at the time of analysis). Sensitivity analyses were conducted to assess the impact of uncertain variables on the disease costs. Farmers surveyed were aware of schistosomiasis in their ruminant livestock and reported hollowing around the eyes, diarrhoea and weight loss as the most common clinical signs in all species. For scenario 1, the median disease costs per year and head of cattle, sheep and goats were estimated at 13,408 XOF, 27,227 XOF and 27,694 XOF, respectively. For scenario 2, the disease costs per year and head of cattle, sheep and goats were estimated at 49,296 XOF, 70,072 XOF and 70,281 XOF, respectively. Our findings suggest that the financial impact of livestock schistosomiasis on traditional subsistence and transhumance farmers is substantial. Consequently, treating livestock schistosomiasis has the potential to generate considerable benefits to farmers and their families. Given the dearth of data in this region, our study serves as a foundation for further in-depth studies to provide estimates of disease impact and as a baseline for future economic analyses. This will also enable One Health economic studies where the burden on both humans and animals is estimated and included in cross-sectoral cost-benefit and cost-effectiveness analyses of disease control strategies.

Biomechanical interactions of Schistosoma mansoni eggs with vascular endothelial cells facilitate egg extravasation.

Yeh, Y., Skinner, D., Criado-Hidalgo, E., Chen, N., Garcia-De Herreros, A., El-Sakkary, N., Liu, L., Zhang, S., Kandasamy, A., Chien, S., Lasheras, J., Del Álamo, J., Caffrey, C.
22-03-2022
PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010309

The eggs of the parasitic blood fluke, Schistosoma, are the main drivers of the chronic pathologies associated with schistosomiasis, a disease of poverty afflicting approximately 220 million people worldwide. Eggs laid by Schistosoma mansoni in the bloodstream of the host are encapsulated by vascular endothelial cells (VECs), the first step in the migration of the egg from the blood stream into the lumen of the gut and eventual exit from the body. The biomechanics associated with encapsulation and extravasation of the egg are poorly understood. We demonstrate that S. mansoni eggs induce VECs to form two types of membrane extensions during encapsulation; filopodia that probe eggshell surfaces and intercellular nanotubes that presumably facilitate VEC communication. Encapsulation efficiency, the number of filopodia and intercellular nanotubes, and the length of these structures depend on the egg's vitality and, to a lesser degree, its maturation state. During encapsulation, live eggs induce VEC contractility and membranous structures formation in a Rho/ROCK pathway-dependent manner. Using elastic hydrogels embedded with fluorescent microbeads as substrates to culture VECs, live eggs induce VECs to exert

significantly greater contractile forces during encapsulation than dead eggs, which leads to 3D deformations on both the VEC monolayer and the flexible substrate underneath. These significant mechanical deformations cause the VEC monolayer tension to fluctuate with the eventual rupture of VEC junctions, thus facilitating egg transit out of the blood vessel. Overall, our data on the mechanical interplay between host VECs and the schistosome egg improve our understanding of how this parasite manipulates its immediate environment to maintain disease transmission.

Correction: Dynamics of serological responses to defined recombinant proteins during Schistosoma mansoni infection in mice before and after the treatment with praziquantel.

Mohammed, E., Nakamura, R., Kalenda, Y., Deloer, S., Moriyasu, T., Tanaka, M., Fujii, Y., Kaneko, S., Hirayama, K., Ibrahim, A., El-Seify, M., Metwally, A., Hamano, S.
22-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010309

[This corrects the article DOI: 10.1371/journal.pntd.0008518.].

Non-typhoidal Salmonella upper limb osteomyelitis and soft tissue abscess leading to a diagnosis of sickle cell anaemia.

Norman, F., Chamorro, S., Tenorio, M., Monge, B., García, A., Comeche, B., Pérez-Molina, J., López-Vélez, R.
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J Travel Med
https://pubmed.ncbi.nlm.nih.gov/34581404

HELMINTHIASES TRANSMISES PAR LE SOL (ASCARIDIOSE, TRICHURIASE, ANKYLOSTOMIASE)

Prevalence of Soil-Transmitted Helminthes and Associated Risk Factors Among People of Ethiopia: A Systematic Review and Meta-Analysis.

Aemiro, A., Menkir, S., Tegen, D., Tola, G.
26-03-2022
Infect Dis (Auckl)
https://doi.org/10.1177/11786337211055437

A Soil-transmitted helminthic infection (STHIs) remains a notable health problem in resource-limited countries. This systematic review and meta-analysis aimed to determine the overall prevalence of STH infections in Ethiopia. Articles written in English were searched from online public databases. Searching terms taken separately and jointly were "prevalence," "soil-transmitted helminths" "nematode," "Geo-helminths," "roundworm," "Necator," "Ancylostoma," "Ascaris," "Trichuris," "hookworm," "whipworm," "*S. strecoralies*," "associated factors," and "Ethiopia." We used STATA version 14 for meta-analysis and Cochran's Q test statistics and the I^2 test for heterogeneity. From 297 reviewed articles 41 fulfilled the inclusion criteria. The pooled prevalence of STH infections in Ethiopia was 36.78% Ascaris lumbricoides had the highest pooled prevalence 17.63%, followed by hook worm12.35%. Trichuris trichiura 7.24% when the prevalence of *S. strecoralies* was 2.16% (95% CI: 0.97-3.35). Age, sex, residence, family education level, lack of shoe wearing habits and open defecation were identified as risk factors for STH infection. Eating unwashed and uncooked fruit and vegetables increased the risk of STH infection by 1.88 times while untrimmed finger nail and lack of hand washing habits increase the risk of STH infection by 1.28 and 3.16 times respectively with 95% CI. Lack of published studies from Afar, Gambela, Somali, and Benshangul gumuz regions may affect the true picture. The other limitation is that the search strategy will be restricted articles published only in the English language but there might be articles that published using another language. Ascaris lumbricoides, hookworms and Trichuris trichiura, are the most prevalent soil-transmitted helminthes infections in Ethiopia. Age, sex, residence, family education level, lack of shoe wearing habits Open defecation untrimmed finger nail and lack of hand washing habits significantly associated with STH infection. When eating unwashed, uncooked fruit and vegetables were not significantly associated with STH infection. Strategic use of anti-helminthic, health education, and adequate sanitation, taking into account this epidemiologic information is helpful in the control of STH infections in Ethiopia.

National mapping of schistosomiasis, soil-transmitted helminthiasis and anaemia in Yemen: Towards better national control and elimination.

Johari, N., Annuzaili, D., El-Talabawy, H., Ba-Break, M., Al-Mekhlafi, A., Al-Eryani, S., Alkohlani, A., Gabrielli, A., Ben-Ismail, R., Alhaidari, S., Muaydh, A., Alshami, R., Al Gunaid, M., Hamed, A., Kamel, N., Palacio, K., Fleming, F., French, M.
25-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010092

Schistosomiasis (SCH) and soil-transmitted helminthiasis (STH) are known to be endemic in Yemen. However, the distribution of both diseases had not previously been assessed by a well-structured national mapping study covering all governorates. The main aim of this study was, therefore, to map the prevalence of SCH and STH in Yemen in order to better inform implementation of effective national control and elimination interventions. The assessment of the distribution of anaemia was also included as a well-known consequence of infection with both SCH and STH. Secondarily, the study aimed to provide a broad indication of the impact of large-scale treatment on the distribution of infection. To achive these

aims, 80,432 children (10-14 years old) from 2,664 schools in 332 of Yemen's 333 districts were included, in 2014, into this national cross-sectional survey. Countrywide, 63.3% (210/332) and 75.6% (251/332) of districts were found to be endemic for SCH and STH respectively. More districts were affected by intestinal than urogenital SCH (54.2% and 31.6% respectively). SCH infection was mostly mild and moderate, with no districts reporting high infection. One quarter (24.4%) of Yemeni districts had high or moderate levels of Ascaris lumbricoides infection. Infection with Trichuris trichiura was the second most common STH (44.9% of districts infected) after A. lumbricoides (68.1%). Hookworm was the least prevalent STH (9.0%). Anaemia was prevalent in 96.4% of districts; it represented a severe public health problem (prevalence ≥ 40%) in 26.5% of districts, and a mild to moderate problem in two thirds of the districts (33.7% and 36.1% respectively). This study provided the first comprehensive mapping of SCH, STH, and anaemia across the country. This formed the basis for evaluating and continuing the national control and elimination programme for these neglected tropical diseases in Yemen.

Gale

Prevention of bacterial complications of scabies using mass drug administration: A population-based, before-after trial in Fiji, 2018-2020.

Thean, L., Romani, L., Engelman, D., Wand, H., Jenney, A., Mani, J., Paka, J., Cua, T., Taole, S., Silai, M., Ashwini, K., Sahukhan, A., Kama, M., Tuicakau, M., Kado, J., Parnaby, M., Carvalho, N., Whitfeld, M., Kaldor, J., Steer, A.
22-03-2022
Lancet Reg Health West Pac
https://doi.org/10.1016/j.lanwpc.2022.100433

Scabies is an important predisposing factor of impetigo which can lead to serious bacterial complications. Ivermectin-based mass drug administration can substantially reduce scabies and impetigo prevalence in endemic settings, but the impact on serious bacterial complications is not known. We conducted a before-after trial in the Northern Division of Fiji (population: 131,914) of mass drug administration for scabies control. Prospective surveillance was conducted from 2018 to 2020. Mass drug administration took place in 2019, involving two doses of oral ivermectin or topical permethrin, delivered alongside diethylcarbamazine and albendazole for lymphatic filariasis. The primary outcomes were incidence of hospitalisations with skin and soft tissue infections, and childhood invasive infections and post-streptococcal sequelae. Secondary outcomes included presentations to primary healthcare with skin infections and community prevalence of scabies and impetigo. The incidence of hospitalisations with skin and soft tissue infections was 17% lower after the intervention compared to baseline (388 vs 467 per 100,000 person-years; incidence rate ratio 0.83, 95% CI, 0.74 to 0.94; $P = 0.002$). There was no difference in incidence of childhood invasive infections and post-streptococcal sequelae. Incidence of primary healthcare presentations with scabies and skin infections was 21% lower (89.2 vs 108 per 1000 person-years, incidence rate ratio, IRR 0.79, 95% CI, 0.78 to 0.82). Crude community prevalence of scabies declined from 14.2% to 7.7% (cluster-adjusted prevalence 12.5% to 8.9%; prevalence ratio 0.71, 95% CI, 0.28 to 1.17). Cluster-adjusted prevalence of impetigo declined from 15.3% to 6.1% (prevalence ratio 0.4, 95% CI, 0.18 to 0.86). Mass drug administration for scabies control was associated with a substantial reduction in hospitalisations for skin and soft tissue infections. National Health and Medical Research Council of Australia and Scobie and Claire Mackinnon Trust.

Health care cost of crusted scabies in Aboriginal communities in the Northern Territory, Australia.

Campbell, M., van der Linden, N., Gardner, K., Dickinson, H., Agostino, J., Dowden, M., O'Meara, I., Scolyer, M., Woerle, H., Viney, R., van Gool, K.
28-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010288

Crusted scabies is a debilitating dermatological condition. Although still relatively rare in the urban areas of Australia, rates of crusted scabies in remote Aboriginal communities in the Northern Territory (NT) are reported to be among the highest in the world. To estimate the health system costs associated with diagnosing, treating and managing crusted scabies. A disease pathway model was developed to identify the major phases of managing crusted scabies. In recognition of the higher resource use required to treat more severe cases, the pathway differentiates between crusted scabies severity grades. The disease pathway model was populated with data from a clinical audit of 42 crusted scabies patients diagnosed in the Top-End of Australia's Northern Territory between July 1, 2016 and May 1, 2018. These data were combined with standard Australian unit costs to calculate the expected costs per patient over a 12-month period, as well as the overall population cost for treating crusted scabies. The expected health care cost per patient diagnosed with crusted scabies is $35,418 Australian dollars (AUD) (95% CI: $27,000 to $43,800), resulting in an overall cost of $1,558,392AUD (95% CI: $1,188,000 to $1,927,200) for managing all patients diagnosed in the Northern Territory in a given year (2018). By far, the biggest component of the health care costs falls on the hospital system. This is the first cost-of-illness analysis for treating crusted scabies. Such analysis will be of value to policy makers and researchers by informing future evaluations of crusted scabies prevention programs and resource allocation decisions. Further research is needed on the wider costs of crusted scabies including non-financial impacts such as the loss in quality of life as well as the burden of care and loss of well-being for patients, families and communities.

The Burrow Ink Test: a Simple Method to Improve the Diagnosis of Scabies.

Del Barrio-Díaz, P., Vera-Kellet, C.
23-03-2022
J Gen Intern Med
https://doi.org/10.1007/s11606-020-06522-6

Oral ivermectin: a feasible alternative to topical therapy of genital scabies.

Fidanzi, C., Janowska, A., Romanelli, M., D'Erme, A., Bagnoni, G., Dini, V.
22-03-2022
Sex Transm Infect
https://pubmed.ncbi.nlm.nih.gov/35318287

[Use of a portable digital microscope in the diagnosis of scabies].

Álvarez Sierra, M., Navarro Fernández, Í.
31-01-2022
Med Clin (Barc)
https://pubmed.ncbi.nlm.nih.gov/35094815

MORSURES DE SERPENT

Antivenom Does Not Cause Snakebite Complications, Withholding it Does.

J Gerardo, C., Godfrey, A., Greene, S.
24-03-2022
Am Surg
https://doi.org/10.1177/00031348221082289

We read with interest the retrospective chart review "Crotalidae Polyvalent Immune Fab and Cost-Effective Management of Hospital Admission for Snakebites" by Bowden, et al. The efficacy of US snake antivenoms has been well established for decades. A randomized double-blind placebo-controlled clinical trial (RCT) has demonstrated Fab antivenom efficacy using patient-centered outcomes such as return of functionality and other patient-reported outcomes. These benefits occurred in a predominantly mildly envenomated patient population in a time-dependent manner. The cost-effectiveness of snake antivenom has been demonstrated globally, but no US cost-effectiveness studies have been published. Based on the evidence hierarchy of evidence-based medicine, the discordance between this study and the RCT merits discussion.