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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Risk Factors for Mortality in Patients with Dengue: A Systematic Review and Meta-Analysis.

Revue de littérature

Lima Chagas, G., Rangel, A., Noronha, L., Veloso, F., Kassar, S., Oliveira, M., Meneses, G., da Silva Junior, G., Daher, E.
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To investigate risk factors for mortality in dengue. Systematic review and meta-analysis searching MEDLINE, Embase, SciELO, LILACS Bireme, and OpenGrey to identify eligible observational studies of patients with dengue, of both genders, aged 14 years or older, that analyzed risk factors associated with mortality and reported adjusted risk measures with their respective confidence intervals (CIs). We estimated the pooled weighted mean difference and 95% CIs with a DerSimonian and Laird random-effects model. Methodological quality was assessed using the Newcastle-Ottawa Scale. Of 1,170 citations reviewed, 18 papers, with a total of 25,851 patients, were included in the systematic review and 12 in the meta-analysis. Severe hepatitis (OR 29.222, 95% CI: 3.876-220.314), dengue shock syndrome (OR 23.575, 95% CI 3.664-151.702), altered mental status (OR 3.76, 95% CI 1.67-8.42), diabetes mellitus (OR 3.698, 95% CI 1.196-11.433), and higher pulse rate (OR 1.039, 95% CI 1.011-1.067) are associated with mortality in patients with dengue. All studies included were classified as having a high quality. Proper identification and management of these risk factors should be considered to improve patient outcomes and reduce the hidden burden of this neglected tropical disease. Future well-designed studies are needed to investigate the association of other clinical, radiological, and laboratorial findings with mortality in dengue, as well as to develop prognostic models based on the risk factors found in our study.

Expression of fatty acid synthase genes and their role in development and arboviral infection of Aedes aegypti.

Chotiwan, N., Brito-Sierra, C., Ramirez, G., Lian, E., Grabowski, J., Graham, B., Hill, C., Perera, R.
27-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05336-1

Fatty acids are the building blocks of complex lipids essential for living organisms. In mosquitoes, fatty acids are involved in cell membrane production, energy conservation and expenditure, innate immunity, development and reproduction. Fatty acids are synthesized by a multifunctional enzyme complex called fatty acid synthase (FAS). Several paralogues of FAS were found in the Aedes aegypti mosquito. However, the molecular characteristics and expression of some of these paralogues have not been investigated. Genome assemblies of Ae. aegypti were analyzed, and orthologues of human FAS was identified. Phylogenetic analysis and in silico molecular characterization were performed to identify the functional domains of the Ae. aegypti FAS (AaFAS). Quantitative analysis and loss-of-function experiments were performed to determine the significance of different AaFAS transcripts in various stages of development, expression following different diets and the impact of AaFAS on dengue virus, serotype 2 (DENV2) infection and transmission. We identified seven putative FAS genes in the Ae. aegypti genome assembly, based on nucleotide similarity to the FAS proteins (tBLASTn) of humans, other mosquitoes and invertebrates. Bioinformatics and molecular analyses suggested that only five of the AaFAS genes produce mRNA and therefore represent complete gene models. Expression levels of AaFAS varied among developmental stages and between male and female Ae. aegypti. Quantitative analyses revealed that expression of AaFAS1, the putative orthologue of the human FAS, was highest in adult females. Transient knockdown (KD) of AaFAS1 did not induce a complete compensation by other AaFAS genes but limited DENV2 infection of Aag2 cells in culture and the midgut of the mosquito. AaFAS1 is the predominant AaFAS in adult mosquitoes. It has the highest amino acid similarity to human FAS and contains all enzymatic domains typical of human FAS. AaFAS1 also facilitated DENV2 replication in both cell culture and in mosquito midguts. Our data suggest that AaFAS1 may play a role in transmission of dengue viruses and could represent a target for intervention strategies.

An ensemble forecast system for tracking dynamics of dengue outbreaks and its validation in China.

Chen, Y., Liu, T., Yu, X., Zeng, Q., Cai, Z., Wu, H., Zhang, Q., Xiao, J., Ma, W., Pei, S., Guo, P.
27-06-2022
PLoS Comput Biol
https://doi.org/10.1371/journal.pcbi.1010218

As a common vector-borne disease, dengue fever remains challenging to predict due to large variations in epidemic size across seasons driven by a number of factors including population susceptibility, mosquito density, meteorological conditions, geographical factors, and human mobility. An ensemble forecast system for dengue fever is first proposed that addresses the difficulty of predicting outbreaks with drastically different scales. The ensemble forecast system based on a susceptible-infected-recovered (SIR) type of compartmental model coupled with a data assimilation method called the ensemble adjusted Kalman filter (EAKF) is constructed to generate real-time forecasts of dengue fever spread dynamics. The model was informed by meteorological and mosquito density information to depict the transmission of dengue virus among human and mosquito populations, and generate predictions. To account for the dramatic variations of outbreak size in different seasons, the effective population size parameter that is sequentially updated to adjust the predicted outbreak scale is introduced into the model. Before

optimizing the transmission model, we update the effective population size using the most recent observations and historical records so that the predicted outbreak size is dynamically adjusted. In the retrospective forecast of dengue outbreaks in Guangzhou, China during the 2011-2017 seasons, the proposed forecast model generates accurate projections of peak timing, peak intensity, and total incidence, outperforming a generalized additive model approach. The ensemble forecast system can be operated in real-time and inform control planning to reduce the burden of dengue fever.

Zika virus infection drives epigenetic modulation of immunity by the histone acetyltransferase CBP of Aedes aegypti.

Amarante, A., da Silva, I., Carneiro, V., Vicentino, A., Pinto, M., Higa, L., Moharana, K., Talyuli, O., Venancio, T., de Oliveira, P., Fantappié, M.
27-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010559

Epigenetic mechanisms are responsible for a wide range of biological phenomena in insects, controlling embryonic development, growth, aging and nutrition. Despite this, the role of epigenetics in shaping insect-pathogen interactions has received little attention. Gene expression in eukaryotes is regulated by histone acetylation/deacetylation, an epigenetic process mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). In this study, we explored the role of the Aedes aegypti histone acetyltransferase CBP (AaCBP) after infection with Zika virus (ZIKV), focusing on the two main immune tissues, the midgut and fat body. We showed that the expression and activity of AaCBP could be positively modulated by blood meal and ZIKV infection. Nevertheless, Zika-infected mosquitoes that were silenced for AaCBP revealed a significant reduction in the acetylation of H3K27 (CBP target marker), followed by downmodulation of the expression of immune genes, higher titers of ZIKV and lower survival rates. Importantly, in Zika-infected mosquitoes that were treated with sodium butyrate, a histone deacetylase inhibitor, their capacity to fight virus infection was rescued. Our data point to a direct correlation among histone hyperacetylation by AaCBP, upregulation of antimicrobial peptide genes and increased survival of Zika-infected-A. aegypti.

Accuracy of the Hammersmith infant neurological examination for the early detection of neurological changes in infants exposed to Zika virus: A case-cohort study.

de Souza, T., Bagne, E., Mizani, R., Rotob, A., Gazeta, R., de Sene Amâncio Zara, A., Jundiaí, C., Passos, S.
24-06-2022
Medicine (Baltimore)
https://doi.org/10.1097/MD.0000000000029488

The Hammersmith infant neurological examination (HINE) is a highly predictive tool for the easy and low-cost detection of cerebral palsy. Between 2015 and 2016, the rapid spread of the Zika virus (ZIKV) in Brazil was responsible for an increase in microcephaly cases. This study aimed to verify the accuracy of the HINE for the early detection of neurological problems in Brazilian babies exposed to ZIKV.This was a cross sectional case-control study of children exposed to ZIKV. This study was part of the Jundiaí ZIKV Cohort. Of a total sample of 782 children, 98 were evaluated (26 in the exposed group and 63 in the control group). We included late preterm infants and term infants who were exposed to the ZIKV and were participants in the ZIKV Cohort study. Student's t-test and stepwise multivariate logistic regression were used to compare groups.Of the 26 items evaluated in the five scored categories of the HINE (cranial nerve function, posture, movements, tone, reflexes, and reactions), only the difference in ankle dorsiflexion between the exposed and the control groups was statistically significant. However, some items showed a significant trend in relation to the control group.Our results demonstrated the importance of early neurological assessment of infants exposed to ZIKV, even in those without a microcephaly diagnosis.

Dengue virus is involved in insulin resistance via the downregulation of IRS-1 by inducing TNF-α secretion.

Liu, X., Liang, Z., Duan, H., Yu, J., Qin, Z., Li, J., Zhu, L., Wu, Q., Xiao, W., Shen, C., Wan, C., Wu, K., Ye, H., Zhang, B., Zhao, W.
22-06-2022
Biochim Biophys Acta Mol Basis Dis
https://pubmed.ncbi.nlm.nih.gov/35752384

During the epidemic, the individuals with underlying diseases usually have a higher rate of mortality. Diabetes is highly prevalent worldwide, making it a frequent comorbidity in dengue fever patients. Therefore, understanding the relationship between dengue virus (DENV) infection and diabetes is important. We first demonstrated that DENV-3 infection down-regulated the expression of IRS-1. In vitro, treatment of HepG2 cells with TNF-α inhibitors and siRNA proved that after DENV-3 infection in HepG2 cells, cellular TNF-α secretion was increased, which negatively regulated IRS-1, thereby leading to an insulin-resistant state. In vivo, DENV-3 induced insulin resistance (IR) in hepatocytes by promoting the secretion of TNF-α and inhibiting the expression of IRS-1 was proved. In vivo approaches also showed that after DENV-3 infection, TNF-α levels in the serum of C57BL/6 mice with insulin resistance increased, and upon TNF-α antagonist III treatment, IRS-1 expression in the liver, reduced by infection, was upregulated. In addition, transcriptomic analysis revealed more negative regulatory events in the insulin receptor signaling pathway after DENV-3 infection. This is the first report of a link between DENV-3 infection and insulin resistance, and it lays a foundation for further research.

Factors impacting severe disease from chikungunya infection: Prioritizing chikungunya vaccine when available.

Grobusch, M., Connor, B.
22-06-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35752291

A recent chikungunya outbreak associated with the occurrence of Aedes vectors (Diptera: Culicidae) in Kassala state, eastern Sudan in 2018.

Siam, H., Elaagip, A., Abrahim, S., Mohammed, M., Noaman, O., Samy, A.
22-06-2022
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/35752225

Aedes aegypti and Ae. albopictus (Diptera: Culicidae) are primary vectors of human arboviral diseases such as dengue, chikungunya, yellow fever, and Zika viruses. Aedes aegypti is well distributed in Sudan, except in Northern and Khartoum states, while Ae. albopictus has not been previously reported. Recently, Eastern Sudan witnessed an unprecedented large outbreak of chikungunya fever between 31 May 2018 and 30 March 2019. The outbreak was composed of four waves; one of them was in Kassala state. Aedes survey in localities of Kassala state (rather than Kassala city) is carried out to assess the possible expansion of the disease in the state. The results showed the presence of immature stages of Aedes spp. in four localities from ten localities. From the four localities that recorded Aedes spp., two localities (Rural Kassala and West Kassala) were reported with chikungunya cases. From this investigation, Ae. albopictus was reported for the first time in Sudan. Also, this investigation showed the importance of conducting entomological surveys with epidemiological surveys during outbreaks of arboviral diseases.

Structure of the Dengue Virus RNA Promoter.

Sun, Y., Varani, G.
24-06-2022
RNA
https://pubmed.ncbi.nlm.nih.gov/35750488

Dengue virus, a single-stranded positive sense RNA virus, is the most prevalent mosquito-borne pathogen in the world. Like all RNA viruses, it uses conserved structural elements within its genome to control essential replicative steps. A 70 nucleotides stem-loop RNA structure (called SLA) found at the 5'-end of the genome of all flaviviruses, functions as the promoter for viral replication. This highly conserved structure interacts with the viral polymerase NS5 to initiate RNA synthesis. Here we report the NMR structure of a monomeric SLA from Dengue virus serotype 1, assembled to high-resolution from independently folded structural elements. The DENV1 SLA has an L-shape structure, where the top and side helices are coaxially-stacked and the bottom helix is roughly perpendicular to them. Because the sequence is highly conserved among different flavivirus genomes, it is likely that the three-dimensional fold and local structure of SLA are also conserved among flaviviruses and required for efficient replication. This work provides structural insight into the Dengue promoter and provides the foundation for the discovery of new antiviral drugs that target this essential replicative step.

Synthesis of baicalein derivatives and evaluation of their antiviral activity against arboviruses.

Qian, X., Zhou, H., Liu, Y., Dong, J., Tang, W., Zhao, P., Tang, H., Jin, Y.
20-06-2022
Bioorg Med Chem Lett
https://pubmed.ncbi.nlm.nih.gov/35738350

Natural plant-derived baicalein which is extracted from Chinese herb Scutellaria baicalensis Georgi belongs to the flavonoid compounds and possesses multiple pharmacological activities. In this study, we designed and synthesized new series of derivatives of baicalein (BE) through catalytic coupling reactions, and screened for their antiviral activity against arboviruses including Chikungunya virus (CHIKV), West Nile virus (WNV) or Zika virus (ZIKV). Our results revealed for the first time that BE and its derivatives had potent anti-CHIKV, anti-WNV and anti-ZIKV effects. And modification of 8 or 4' position could lead to obtain potent antiviral compounds against CHIKV, WNV and ZIKV with lower cytotoxicity. Among the baicalein derivatives, C3 and F3 showed the most potent antiviral activities against CHIKV, WNV and ZIKV, which were 5-10 times more potent than baicalein. Our findings will provide research basis for the development of baicalein derivatives as effective antiviral agents.

Efficacy of a spatial repellent for control of *Aedes*-borne virus transmission: A cluster-randomized trial in Iquitos, Peru.

Morrison, A., Reiner, R., Elson, W., Astete, H., Guevara, C., Del Aguila, C., Bazan, I., Siles, C., Barrera, P., Kawiecki, A., Barker, C., Vasquez, G., Escobedo-Vargas, K., Flores-Mendoza, C., Huaman, A., Leguia, M., Silva, M., Jenkins, S., Campbell, W., Abente, E., Hontz, R., Paz-Soldan, V., Grieco, J., Lobo, N., Scott, T., Achee, N.
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Over half the world's population is at risk for viruses transmitted by *Aedes* mosquitoes, such as dengue and Zika. The primary vector, *Aedes aegypti*, thrives in urban environments. Despite decades of effort, cases and geographic range of *Aedes*-borne viruses (ABVs) continue to expand. Rigorously proven vector control interventions that measure protective efficacy against ABV diseases are limited to *Wolbachia* in a single trial in Indonesia and do not include any chemical intervention. Spatial repellents, a new option for efficient deployment, are designed to decrease human exposure to ABVs by releasing active ingredients into the air that disrupt mosquito-human contact. A parallel, cluster-

randomized controlled trial was conducted in Iquitos, Peru, to quantify the impact of a transfluthrin-based spatial repellent on human ABV infection. From 2,907 households across 26 clusters (13 per arm), 1,578 participants were assessed for seroconversion (primary endpoint) by survival analysis. Incidence of acute disease was calculated among 16,683 participants (secondary endpoint). Adult mosquito collections were conducted to compare *Ae. aegypti* abundance, blood-fed rate, and parity status through mixed-effect difference-in-difference analyses. The spatial repellent significantly reduced ABV infection by 34.1% (one-sided 95% CI lower limit, 6.9%; one-sided *P* value = 0.0236, z = 1.98). *Aedes aegypti* abundance and blood-fed rates were significantly reduced by 28.6 (95% CI 24.1%, ∞); z = -9.11) and 12.4% (95% CI 4.2%, ∞); *z* = -2.43), respectively. Our trial provides conclusive statistical evidence from an appropriately powered, preplanned cluster-randomized controlled clinical trial of the impact of a chemical intervention, in this case a spatial repellent, to reduce the risk of ABV transmission compared to a placebo.

Intron-derived small RNAs for silencing viral RNAs in mosquito cells.

Tng, P., Carabajal Paladino, L., Anderson, M., Adelman, Z., Fragkoudis, R., Noad, R., Alphey, L.
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Aedes aegypti and Ae. albopictus are the main vectors of mosquito-borne viruses of medical and veterinary significance. Many of these viruses have RNA genomes. Exogenously provided, e.g. transgene encoded, small RNAs could be used to inhibit virus replication, breaking the transmission cycle. We tested, in Ae. aegypti and Ae. albopictus cell lines, reporter-based strategies for assessing the ability of two types of small RNAs to inhibit a chikungunya virus (CHIKV) derived target. Both types of small RNAs use a Drosophila melanogaster pre-miRNA-1 based hairpin for their expression, either with perfect base-pairing in the stem region (shRNA-like) or containing two mismatches (miRNA-like). The pre-miRNA-1 stem loop structure was encoded within an intron; this allows co-expression of one or more proteins, e.g. a fluorescent protein marker tracking the temporal and spatial expression of the small RNAs in vivo. Three reporter-based systems were used to assess the relative silencing efficiency of ten shRNA-like siRNAs and corresponding miRNA-like designs. Two systems used a luciferase reporter RNA with CHIKV RNA inserted either in the coding sequence or within the 3' UTR. A third reporter used a CHIKV derived split replication system. All three reporters demonstrated that while silencing could be achieved with both miRNA-like and shRNA-like designs, the latter were substantially more effective. Dcr-2 was required for the shRNA-like siRNAs as demonstrated by loss of inhibition of the reporters in Dcr-2 deficient cell lines. These positive results in cell culture are encouraging for the potential use of this pre-miRNA-1-based system in transgenic mosquitoes.

Insights into the product release mechanism of dengue virus NS3 helicase.

Adler, N., Cababie, L., Sarto, C., Cavasotto, C., Gebhard, L., Estrin, D., Gamarnik, A., Arrar, M., Kaufman, S.
23-06-2022
Nucleic Acids Res
https://pubmed.ncbi.nlm.nih.gov/35736223

The non-structural protein 3 helicase (NS3h) is a multifunctional protein that is critical in RNA replication and other stages in the flavivirus life cycle. NS3h uses energy from ATP hydrolysis to translocate along single stranded nucleic acid and to unwind double stranded RNA. Here we present a detailed mechanistic analysis of the product release stage in the catalytic cycle of the dengue virus (DENV) NS3h. This study is based on a combined experimental and computational approach of product-inhibition studies and free energy calculations. Our results support a model in which the catalytic cycle of ATP hydrolysis proceeds through an ordered sequential mechanism that includes a ternary complex intermediate (NS3h-Pi-ADP), which evolves releasing the first product, phosphate (Pi), and subsequently ADP. Our results indicate that in the product release stage of the DENV NS3h a novel open-loop conformation plays an important role that may be conserved in NS3 proteins of other flaviviruses as well.

Parentage Assignment Using Microsatellites Reveals Multiple Mating in Aedes aegypti (Diptera: Culicidae): Implications for Mating Dynamics.

Pimid, M., Krishnan, K., Ahmad, A., Mohd Naim, D., Chambers, G., Mohd Nor, S., Ab Majid, A.
23-06-2022
J Med Entomol
https://pubmed.ncbi.nlm.nih.gov/35733165

The mosquito Aedes aegypti is the primary vector of the dengue, yellow fever, and chikungunya viruses. Evidence shows that Ae. aegypti males are polyandrous whereas Ae. aegypti females are monandrous in mating. However, the degree to which Ae. aegypti males and females can mate with different partners has not been rigorously tested. Therefore, this study examined the rates of polyandry via parentage assignment in three sets of competitive mating experiments using wild-type male and female Ae. aegypti. Parentage assignment was monitored using nine microsatellite DNA markers. All Ae. aegypti offspring were successfully assigned to parents with 80% or 95% confidence using CERVUS software. The results showed that both male and female Ae. aegypti mated with up to 3-4 different partners. Adults contributed differentially to the emergent offspring, with reproductive outputs ranging from 1 to 25 viable progeny. This study demonstrates a new perspective on the capabilities of male and female Ae. aegypti in mating. These findings are significant because successful deployment of reproductive control methods using genetic modification or sterile Ae. aegypti must consider the following criteria regarding their mating fitness: 1) choosing Ae. aegypti males that can mate with many different females; 2) testing how transformed Ae.

aegypti male perform with polyandrous females; and 3) prioritizing the selection of polyandrous males and/or females Ae. aegypti that have the most offspring.

Zika Virus Strains and Dengue Virus Induce Distinct Proteomic Changes in Neural Stem Cells and Neurospheres.

Nascimento, J., Gouvêa-Junqueira, D., Zuccoli, G., Pedrosa, C., Brandão-Teles, C., Crunfli, F., Antunes, A., Cassoli, J., Karmirian, K., Salerno, J., de Souza, G., Muraro, S., Proenca-Módena, J., Higa, L., Tanuri, A., Garcez, P., Rehen, S., Martins-de-Souza, D.
22-06-2022
Mol Neurobiol
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Brain abnormalities and congenital malformations have been linked to the circulating strain of Zika virus (ZIKV) in Brazil since 2016 during the microcephaly outbreak; however, the molecular mechanisms behind several of these alterations and differential viral molecular targets have not been fully elucidated. Here we explore the proteomic alterations induced by ZIKV by comparing the Brazilian (Br ZIKV) and the African (MR766) viral strains, in addition to comparing them to the molecular responses to the Dengue virus type 2 (DENV). Neural stem cells (NSCs) derived from induced pluripotent stem (iPSCs) were cultured both as monolayers and in suspension (resulting in neurospheres), which were then infected with ZIKV (Br ZIKV or ZIKV MR766) or DENV to assess alterations within neural cells. Large-scale proteomic analyses allowed the comparison not only between viral strains but also regarding the two- and three-dimensional cellular models of neural cells derived from iPSCs, and the effects on their interaction. Altered pathways and biological processes were observed related to cell death, cell cycle dysregulation, and neurogenesis. These results reinforce already published data and provide further information regarding the biological alterations induced by ZIKV and DENV in neural cells.

Characterization of the RNA-dependent RNA polymerase from Chikungunya virus and discovery of a novel ligand as a potential drug candidate.

Freire, M., Basso, L., Mendes, L., Mesquita, N., Mottin, M., Fernandes, R., Policastro, L., Godoy, A., Santos, I., Ruiz, U., Caruso, I., Sousa, B., Jardim, A., Almeida, F., Gil, L., Andrade, C., Oliva, G.
22-06-2022
Sci Rep
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Chikungunya virus (CHIKV) is the causative agent of Chikungunya fever, an acute febrile and arthritogenic illness with no effective treatments available. The development of effective therapeutic strategies could be significantly accelerated with detailed knowledge of the molecular components behind CHIKV replication. However, drug discovery is hindered by our incomplete understanding of their main components. The RNA-dependent RNA-polymerase (nsP4-CHIKV) is considered the key enzyme of the CHIKV replication complex and a suitable target for antiviral therapy. Herein, the nsP4-CHIKV was extensively characterized through experimental and computational biophysical methods. In the search for new molecules against CHIKV, a compound designated LabMol-309 was identified as a strong ligand of the nsp4-CHIKV and mapped to bind to its active site. The antiviral activity of LabMol-309 was evaluated in cellular-based assays using a CHIKV replicon system and a reporter virus. In conclusion, this study highlights the biophysical features of nsP4-CHIKV and identifies a new compound as a promising antiviral agent against CHIKV infection.

Sensitivity of wMel and wAlbB Wolbachia infections in Aedes aegypti Puducherry (Indian) strains to heat stress during larval development.

Gunasekaran, K., Sadanandane, C., Panneer, D., Kumar, A., Rahi, M., Dinesh, S., Vijayakumar, B., Krishnaraja, M., Subbarao, S., Jambulingam, P.
21-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05345-0

ICMR-Vector Control Research Centre, Puducherry, India, developed two colonies of Aedes aegypti infected with wMel and wAlbB Wolbacia strains called Ae. aegypti (Pud) lines for dengue control. The sensitivity of wMel and wAlbB strains in Ae. aegypti (Pud) lines to heat stress was studied. wMel and wAlbB infected and uninfected Ae. aegypti larvae (first to fourth instars) were reared in the laboratory to adults at 26 °C, 30 °C, 36 °C and 40 °C constant temperatures and also 26-30 °C, 26-36 °C and 26-40 °C diurnal cyclic temperatures. The adults were tested for Wolbachia infection. Experiments were also carried out rearing the larvae under simulated field conditions in summer (April and June) under sunlight using fully open and half open bowls and also under sunlight and natural shade. At 36 °C and 40 °C constant temperatures, complete larval mortality was observed. At 30 °C and 26 °C, no larval mortality occurred, but Wolbachia density was relatively low in wMel infected males compared to control (maintained at 26±1 °C). At diurnal cyclic temperature of 26-40 °C, Wolbachia density was reduced in males of both the (Pud) lines, but not in females. At 26-36 °C, reduction in Wolbachia density was observed in wMel males but not in wAlbB males. At 26-30 °C, no significant reduction in Wolbachia density was observed with wMel and wAlbB strains. In simulated field conditions (April), under sunlight, the daytime water temperature reached a maximum of 35.7 °C in both full and half open bowls. No larval mortality occurred. Wolbachia frequency and density was reduced in wMel-infected Ae. aegypti (Pud) males from both type of bowls and in females from full open bowls, and in wAlbB males from half open bowls. In June, rearing of larvae under sunlight, the first-instar larvae experienced a maximum daytime water temperature of>38 °C that caused complete mortality. No larval mortality was observed in bowls kept under shade (<32 °C). Exposure of larvae to higher rearing temperatures in the laboratory and simulated-field conditions reduced the densities of wMel and wAlbB strains particularly in males, but the impact was more

pronounced for wMel strain. The actual effect of heat stress on the stability of these two Wolbachia strains needs to be tested under natural field conditions.

Studies on the antiviral activity of chebulinic acid against dengue and chikungunya viruses and in silico investigation of its mechanism of inhibition.

Thomas, N., Patil, P., Sharma, A., Kumar, S., Singh, V., Alagarasu, K., Parashar, D., Tapryal, S.
21-06-2022
Sci Rep
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Chebulinic acid (CA), originally isolated from the flower extract of the plant Terminalia chebula, has been shown to inhibit infection of herpes simplex virus-2 (HSV-2), suggestively by inhibiting the host entry step of viral infection. Like HSV-2, the dengue virus (DENV) and chikungunya virus (CHIKV) also use receptor glycosaminoglycans (GAG) to gain host entry, therefore, the activity of CA was tested against these viruses. Co-treatment of 8 µM CA with DENV-2 caused 2 log decrease in the virus titer (4.0 $\log_{10}$FFU/mL) at 120 h post infection, compared to virus control (5.95 $\log_{10}$FFU/mL). In contrast, no inhibitory effect of CA was observed against CHIKV infection under any condition. The mechanism of action of CA was investigated in silico by employing DENV-2 and CHIKV envelope glycoproteins. During docking, CA demonstrated equivalent binding at multiple sites on DENV-2 envelope protein, including GAG binding site, which have previously been reported to play a crucial role in host attachment and fusion, indicating blocking of these sites. However, CA did not show binding to the GAG binding site on envelope protein-2 of CHIKV. The in vitro and in silico findings suggest that CA possesses the ability to inhibit DENV-2 infection at the entry stage of its infection cycle and may be developed as a potential therapeutic agent against it.

Neurological Complications of Dengue Fever.

Revue de littérature

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Curr Neurol Neurosci Rep
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To discuss the neurological complications of dengue virus (DENV) infection and their pathogenesis. Include recognition of the four different serotypes of DENV and their epidemiology as well as recognition of the expanded dengue syndrome encompassing multisystem involvement in the severe form of the disease including involvement of the central nervous system (CNS). DENV is a neurotropic virus with the ability to infect the supporting cells of the CNS. Neural injury during the acute stage of the infection results from direct neuro-invasion and/or the phenomenon of antibody-dependent enhancement, resulting in plasma leakage and coagulopathy. Immune mechanisms have been implicated in the development of the delayed neurological sequelae through molecular mimicry. A myriad of neurological syndromes has been described as a result of the involvement of the CNS, the peripheral nervous system (PNS), or both. Neurological manifestations in DENV infection are increasingly being recognized, some of which are potentially fatal if not treated promptly. DENV encephalopathy and encephalitis should be considered in the differential diagnosis of other acute febrile encephalopathies, autoimmune encephalitides, and in cases of encephalopathy/encephalitis related to SARS-CoV2 infection, especially in dengue-endemic areas. Acute disseminated encephalomyelitis (ADEM) may be occasionally encountered. Clinicians should be knowledgeable of the expanded dengue syndrome characterized by the concurrent compromise of cardiac, neurological, gastrointestinal, renal, and hematopopoietic systems. Isolated cranial nerve palsies occur rather uncommonly and are often steroid responsive. These neuropathies may result from the direct involvement of cranial nerve nuclei or nerve involvement or may be immune-mediated. Even if the diagnosis of dengue is confirmed, it is absolutely imperative to exclude other well-known causes of isolated cranial nerve palsies. Ischemic and hemorrhagic strokes may occur following dengue fever. The pathogenesis may be beyond the commonly observed thrombocytopenia and include cerebral vasculitis. Involvement of ocular blood vessels may cause maculopathy or retinal hemorrhages. Posterior reversible encephalopathy syndrome (PRES) is uncommon and possibly related to dysregulated cytokine release phenomena. Lastly, any patient developing acute neuromuscular weakness during the course or within a fortnight of remission from dengue fever must be screened for acute inflammatory demyelinating polyneuropathy (AIDP), hypokalemic paralysis, or acute myositis. Rarely, a Miller-Fisher-like syndrome with negative anti-GQ1b antibody may develop.

Smartphone clip-on instrument and microfluidic processor for rapid sample-to-answer detection of Zika virus in whole blood using spatial RT-LAMP.

Jankelow, A., Lee, H., Wang, W., Hoang, T., Bacon, A., Sun, F., Chae, S., Kindratenko, V., Koprowski, K., Stavins, R., Ceriani, D., Engelder, Z., King, W., Do, M., Bashir, R., Valera, E., Cunningham, B.
21-06-2022
Analyst
https://doi.org/10.1039/d2an00438k

Rapid, simple, inexpensive, accurate, and sensitive point-of-care (POC) detection of viral pathogens in bodily fluids is a vital component of controlling the spread of infectious diseases. The predominant laboratory-based methods for sample processing and nucleic acid detection face limitations that prevent them from gaining wide adoption for POC applications in low-resource settings and self-testing scenarios. Here, we report the design and characterization of an integrated system for rapid sample-to-answer detection of a viral pathogen in a droplet of whole blood comprised of a 2-stage microfluidic cartridge for sample processing and nucleic acid amplification, and a clip-on detection instrument that

interfaces with the image sensor of a smartphone. The cartridge is designed to release viral RNA from Zika virus in whole blood using chemical lysis, followed by mixing with the assay buffer for performing reverse-transcriptase loop-mediated isothermal amplification (RT-LAMP) reactions in six parallel microfluidic compartments. The battery-powered handheld detection instrument uniformly heats the compartments from below, and an array of LEDs illuminates from above, while the generation of fluorescent reporters in the compartments is kinetically monitored by collecting a series of smartphone images. We characterize the assay time and detection limits for detecting Zika RNA and gamma ray-deactivated Zika virus spiked into buffer and whole blood and compare the performance of the same assay when conducted in conventional PCR tubes. Our approach for kinetic monitoring of the fluorescence-generating process in the microfluidic compartments enables spatial analysis of early fluorescent "bloom" events for positive samples, in an approach called "Spatial LAMP" (S-LAMP). We show that S-LAMP image analysis reduces the time required to designate an assay as a positive test, compared to conventional analysis of the average fluorescent intensity of the entire compartment. S-LAMP enables the RT-LAMP process to be as short as 22 minutes, resulting in a total sample-to-answer time in the range of 17-32 minutes to distinguish positive from negative samples, while demonstrating a viral RNA detection as low as 2.70×10^2 copies per µl, and a gamma-irradiated virus of 10^3 virus particles in a single 12.5 µl droplet blood sample.

Mitigating the risk of transfusion-transmitted infections with vector-borne agents solely by means of pathogen reduction.

Stramer, S., Lanteri, M., Brodsky, J., Foster, G., Krysztof, D., Groves, J., Townsend, R., Notari, E., Bakkour, S., Stone, M., Simmons, G., Spencer, B., Tonnetti, L., Busch, M.
21-06-2022
Transfusion
https://doi.org/10.1111/trf.16950

This study evaluated whether pathogen reduction technology (PRT) in plasma and platelets using amotosalen/ultraviolet A light (A/UVA) or in red blood cells using amustaline/glutathione (S-303/GSH) may be used as the sole mitigation strategy preventing transfusion-transmitted West Nile (WNV), dengue (DENV), Zika (ZIKV), and chikungunya (CHIKV) viral, and Babesia microti, Trypanosoma cruzi, and Plasmodium parasitic infections. Antibody (Ab) status and pathogen loads (copies/mL) were obtained for donations from US blood donors testing nucleic acid (NAT)-positive for WNV, DENV, ZIKV, CHIKV, and B. microti. Infectivity titers derived from pathogen loads were compared to published PRT $\log_{10}$ reduction factors (LRF); LRFs were also reviewed for Plasmodium and T. cruzi. The potential positive impact on donor retention following removal of deferrals from required questioning and testing for WNV, Babesia, Plasmodium, and T. cruzi was estimated for American Red Cross (ARC) donors. A/UVA and S-303/GSH reduced infectivity to levels in accordance with those recognized by FDA as suitable to replace testing for all agents evaluated. If PRT replaced deferrals resulting from health history questions and/or NAT for WNV, Babesia, Plasmodium, and T. cruzi, 27,758 ARC donors could be retained allowing approximately 50,000 additional donations/year based on 1.79 donations/donor for calendar year 2019 (extrapolated to an estimated 125,000 additional donations nationally). Pathogen loads in donations from US blood donors demonstrated that robust PRT may provide an opportunity to replace deferrals associated with donor questioning and NAT for vector-borne agents allowing for significant donor retention and likely increased blood availability.

Cross-reactive antibodies facilitate innate sensing of dengue and Zika viruses.

Aisenberg, L., Rousseau, K., Cascino, K., Massaccesi, G., Aisenberg, W., Luo, W., Muthumani, K., Weiner, D., Whitehead, S., Chattergoon, M., Durbin, A., Cox, A.
22-06-2022
JCI Insight
https://doi.org/10.1172/jci.insight.151782

The Aedes aegypti mosquito transmits both dengue virus (DENV) and Zika virus (ZIKV) . Individuals in endemic areas are at risk for infection with both viruses, as well as for repeated DENV infection. In the presence of anti-DENV antibodies, outcomes of secondary DENV infection range from mild to life threatening. Furthermore, the role of cross-reactive antibodies on the course of ZIKV infection remains unclear. We assessed the ability of cross-reactive DENV mAbs or polyclonal immunoglobulin isolated after DENV vaccination to upregulate type I IFN production by plasmacytoid DCs (pDCs) in response to both heterotypic DENV- and ZIKV-infected cells. We found a range in the ability of antibodies to increase pDC IFN production and a positive correlation between IFN production and the ability of an antibody to bind to the infected cell surface. Engagement of Fc receptors on the pDC and engagement of epitope on the infected cell by the Fab portion of the same antibody molecule was required to mediate increased IFN production by providing specificity to and promoting pDC sensing of DENV or ZIKV. This represents a mechanism independent of neutralization by which preexisting cross-reactive DENV antibodies could protect a subset of individuals from severe outcomes during secondary heterotypic DENV or ZIKV infection.

RAGE

Safety and immunogenicity of human rabies vaccine for the Chinese population after PEP: A systematic review and meta-analysis.

Revue de littérature

Wang, L., Zhang, J., Meng, S., Ge, L., You, Y., Xu, Q., Wang, H., Yang, J., Wang, S., Wu, H.
21-06-2022
Vaccine
https://pubmed.ncbi.nlm.nih.gov/35750539

To evaluate the safety and immunogenicity of rabies vaccine for human use after post-exposure in China. A systematic search was performed from PubMed, EMBASE, CNKI and Cochrane Library database, supplemented by manual retrieval. According to the inclusion and exclusion criteria, a meta-analysis was performed using Stata 16.0 software after independent literature screening, data extraction and quality assessment by two evaluators. A total of 32 studies were included. It was found that rabies vaccination after PEP could induce the body to produce sufficient RVNA. Both Essen and Zagreb regimens showed good immunogenicity, with no significant difference in systemic events and local events after PEP, but a relatively high incidence of local and systemic events after PEP under the Zagreb regimen. For the Chinese population, rabies vaccination after PEP has shown relatively a good immune efficacy and acceptable safety for preventing human rabies. The survey also found that the Zagreb regimen was comparable to the Essen regimen in terms of rabies prophylaxis with an acceptable safety profile.

Quantitative risk assessment of rabies being introduced into mainland France through worldwide noncommercial dog and cat movements.

Crozet, G., Rivière, J., Rapenne, E., Cliquet, F., Robardet, E., Dufour, B.
21-06-2022
Risk Anal
https://doi.org/10.1111/risa.13976

France has been rabies-free among nonflying mammals since 2001. Despite this status, the rabies virus has been introduced several times through noncommercial pet movements, posing a threat of infection by this 100%-lethal zoonosis among local animal and human populations. To quantify the risk of rabies being introduced through worldwide noncommercial dog and cat movements, we performed a quantitative risk assessment using stochastic scenario tree modeling. The mean annual probability of at least one rabies introduction incident was 0.35 (median: 0.24, 90% prediction interval (PI) [0.04; 0.98]) and the mean annual number of rabies-infected pets introduced through pet movements was 0.96 (median: 0.27, 90% PI [0.04; 3.88]). These results highlight a nonnegligible, even high risk due to the associated consequences of such events. In alternative scenario testing, preventive anti-rabies vaccination proved to be an effective measure since removing the vaccination requirement led to a > 15-fold increase in risk. The serological testing requirement had less of an effect (approximately two-fold increase when removed) and the posttest waiting period to ensure that antibodies were not linked to an infection had a negligible effect. Any change in pet owner compliance, especially regarding vaccination, could have a major impact on the risk. This study also shows that reinforced border control staff training could be more effective in reducing risk than more frequent checks. These results provide quantitative data for assessing the probability of the rabies virus entering France, and could help policymakers decrease this risk in rabies-free areas.

TRACHOME

To eliminate trachoma: Azithromycin mass drug administration coverage and associated factors among adults in Goro district, Southeast Ethiopia.

Feyisa, T., Bekele, D., Tura, B., Adem, A., Nugusu, F.
27-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010169

Globally, although effective prevention strategies and treatment are available, trachoma remains the major cause of infectious loss of sight. Trachoma is a predominant neglected disease in Ethiopia, and there is a 40.4% prevalence of active trachoma in the Goro district, Southeast Ethiopia. World Health Organization (WHO) recommends azithromycin mass treatment of at least 80% coverage to eliminate trachoma, even though the coverage of azithromycin mass treatment has not been studied yet in depth. Thus, this study aimed to assess the coverage and factors influencing azithromycin mass treatment uptake among adults in Goro district, Southeast Ethiopia. A community-based cross-sectional study was conducted from April 1st to April 30th, 2021 among all adults aged 15 years old and above. The multistage sampling technique was used to select 593 study respondents. A structured interviewer-administered questionnaire was used. Data were entered into Epi-Data version 3.1 and analyzed using SPSS version 23.0 software. Descriptive analysis and binary logistic regression analysis were used to analyze the data. Adjusted odds ratios (AOR) along with a 95% confidence interval (CI) and p-value < 0.05 were used to declare the strength and the significance of association, respectively. Five hundred and seventy eight study participants with a 97% response rate were included. The proportion of azithromycin mass drug administration coverage was found to be 75.80%; 95% CI: (72%-79%) in this study. Having better knowledge about trachoma (AOR = 2.36; 95% CI: 1.19-4.70), having better knowledge about azithromycin mass treatment (AOR = 4.19; 95% CI: 2.19-7.98), being educated (AOR = 7.20; 95% CI: 1.02-51.09), a campaign conducted at the quiet time (off-harvesting/planting season) (AOR = 6.23; 95% CI: 3.23-11.98), heard about the serious adverse effect from others (AOR = 0.25; 95% CI: 0.10-0.59) and being a volunteer to take azithromycin in the next campaign (AOR = 5.46; 95% CI: 2.76-10.79) were significantly associated with azithromycin mass drug administration coverage. The proportion of azithromycin mass treatment coverage of this study was lower than the WHO minimum target coverage. Thus, strengthening

awareness, enhancing azithromycin mass trachoma treatment messages, and conducting campaigns off-season outside of harvesting and planting time should be prioritized in the future to meet the 2030 Sustainable Development Goal (SDG) target.

ULCERE DE BURULI

Development of an antibiotics delivery system for topical treatment of the neglected tropical disease Buruli ulcer.

Mendes, A., Rebelo, R., Aroso, I., Correlo, V., Fraga, A., Pedrosa, J., Marques, A.
24-06-2022
Int J Pharm
https://pubmed.ncbi.nlm.nih.gov/35760261

Skin infection by Mycobacterium ulcerans causes Buruli ulcer (BU) disease, a serious condition that significantly impact patient' health and quality of life and can be very difficult to treat. Treatment of BU is based on daily systemic administration of antibiotics for at least 8 weeks and presents drawbacks associated with the mode and duration of drug administration and potential side effects. Thus, new therapeutic strategies are needed to improve the efficacy and modality of BU therapeutics, resulting in a more convenient and safer antibiotic regimen. Hence, we developed a dual delivery system based on poly(hydroxybutyrate-co-hydroxyvalerate) (PHBV) microparticles and a gellan gum (GG) hydrogel for delivery of rifampicin (RIF) and streptomycin (STR), two antibiotics used for BU treatment. RIF was successfully loaded into PHBV microparticles, with an encapsulation efficiency of 43%, that also revealed a mean size of 10 µm, spherical form and rough topography. These microparticles were further embedded in a GG hydrogel containing STR. The resultant hydrogel showed a porous microstructure that conferred a high water retention capability (superior to 2000%) and a controlled release of both antibiotics. Also, biological studies revealed antibacterial activity against M. ulcerans, and a good cytocompatibility in a fibroblast cell line. Thus, the proposed drug delivery system can constitute a potential topical approach for treatment of skin ulcers caused by BU disease.

PIAN

LEPRE

Hansenapp: development of a mobile application to assist primary healthcare providers to control leprosy.

Matos, D., Torres, M., da Silva, L., Dos Santos, C., de Oliveira, F., de Araújo, M., de Oliveira Serra, M.
27-06-2022
Trop Med Int Health
https://doi.org/10.1111/tmi.13795

To describe the development and validation of a mobile application to assist health professionals in the management of patients with leprosy and surveillance of contacts in primary healthcare. A methodological and developmental study was conducted in three phases: integrative literature review, mobile application development, and application validation by health professionals. The construction of the application was supported by the literature review, Nielsen's heuristics, and expert validation. Five experts individually analyzed the prototype draft and performed two rounds of iterations to refine their recommendations. The validation step was performed by consulting health professionals working in primary healthcare, who evaluated the application for relevance, clarity and usability using a questionnaire based on task-technology fit theory. The mobile app's content, navigation methods, and interaction were refined based on the discussions with experts. Their recommendations were applied, and the mobile app was revised until the final version was approved. Content validity indexes of 0.94 ($p = 0.007$), 0.99 ($p > 0.0001$), and 0.93 ($p = 0.01$) were obtained. The developed application is a technological tool that could assist primary healthcare providers in dealing with leprosy patients and their contacts in terms of management, planning, monitoring, evaluation, treatment, and follow-up, in addition to leprosy control actions.

The two extremes of Hansen's disease-Different manifestations of leprosy and their biological consequences in an Avar Age (late 7th century CE) osteoarchaeological series of the Duna-Tisza Interfluve (Kiskundorozsma-Daruhalom-dűlő II, Hungary).

Spekker, O., Tihanyi, B., Kis, L., Váradi, O., Donoghue, H., Minnikin, D., Szalontai, C., Vida, T., Pálfi, G., Marcsik, A., Molnár, E.
23-06-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265416

To give an insight into the different manifestations of leprosy and their biological consequences in the Avar Age of the Hungarian Duna-Tisza Interfluve, two cases from the 7th-century-CE osteoarchaeological series of Kiskundorozsma-Daruhalom-dűlő II (Hungary; n = 94) were investigated. Based on the macromorphology of the bony changes indicative of

Hansen's disease, KD271 (a middle-aged male) and KD520 (a middle-aged female) represent the two extremes of leprosy. KD271 appears to have an advanced-stage, long-standing near-lepromatous or lepromatous form of the disease, affecting not only the rhinomaxillary region but also both upper and lower limbs. This has led to severe deformation and disfigurement of the involved anatomical areas of the skeleton, resulting in his inability to perform the basic activities of daily living, such as eating, drinking, grasping, standing or walking. The skeleton of KD520 shows no rhinomaxillary lesions and indicates the other extreme of leprosy, a near-tuberculoid or tuberculoid form of the disease. As in KD271, Hansen's disease has resulted in disfigurement and disability of both of the lower limbs of KD520; and thus, the middle-aged female would have experienced difficulties in standing, walking, and conducting occupational physical activities. KD271 and KD520 are amongst the very few published cases with leprosy from the Avar Age of the Hungarian Duna-Tisza Interfluve, and the only examples with detailed macromorphological description and differential diagnoses of the observed leprous bony changes. The cases of these two severely disabled individuals, especially of KD271 - who would have required regular and substantial care from others to survive-imply that in the Avar Age community of Kiskundorozsma-Daruhalom-dűlő II there was a willingness to care for people in need.

Associated factors study into the belated screening for leprosy in Benin.

Gnimavo, R., Sopoh, G., Djossou, P., Anagonou, E., Ayélo, G., Wadagni, A., Barogui, Y., Houezo, J., Johnson, R.
23-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010533

In the absence of early treatment, leprosy, a neglected tropical disease, due to Mycobacterium leprae or Hansen Bacillus, causes irreversible grade 2 disability (G2D) numerous factors related to the individual, the community and the health care system are believed to be responsible for its late detection and management. This study aims to investigate the factors associated with belated screening for leprosy in Benin. This was a cross-sectional, descriptive, and analytical study conducted from January 1 to June 31, 2019, involving all patients and staff in leprosy treatment centers and public peripheral level health structures in Benin. The dependent variable of the study was the presence or not of G2D, reflecting late or early screening. We used a logistic regression model, at the 5% threshold, to find the factors associated with late leprosy screening. The fit of the final model was assessed with the Hosmer-Lemeshow test. A number of 254 leprosy patients were included with a mean age of 48.24 ± 18.37 years. There was a male dominance with a sex ratio of 1.23 (140/114). The proportion of cases with G2D was 58.27%. Associated factors with its belated screening in Benin were (OR; 95%CI; p) the fear of stigma related to leprosy (8.11; 3.3-19.94; <0.001), multiple visits to traditional healers (5.20; 2.73-9.89; <0.001) and multiple visits to hospital practitioners (3.82; 2.01-7.27; <0.001). The unawareness of leprosy by 82.69% of the health workers so as the permanent decrease in material and financial resources allocated to leprosy control were identified as factors in link with the health system that helps explain this late detection. This study shows the need to implement strategies in the control programs to strengthen the diagnostic abilities of health workers, to improve the level of knowledge of the population on the early signs and symptoms of leprosy, to reduce stigmatization and to ban all forms of discrimination against leprosy patients.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Diagnosis of animal trypanosomoses: proper use of current tools and future prospects.

Revue de littérature

Desquesnes, M., Sazmand, A., Gonzatti, M., Boulangé, A., Bossard, G., Thévenon, S., Gimonneau, G., Truc, P., Herder, S., Ravel, S., Sereno, D., Waleckx, E., Jamonneau, V., Jacquiet, P., Jittapalapong, S., Berthier, D., Solano, P., Hébert, L.
27-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05352-1

Reliable diagnostic tools are needed to choose the appropriate treatment and proper control measures for animal trypanosomoses, some of which are pathogenic. Trypanosoma cruzi, for example, is responsible for Chagas disease in Latin America. Similarly, pathogenic animal trypanosomoses of African origin (ATAO), including a variety of Trypanosoma species and subspecies, are currently found in Africa, Latin America and Asia. ATAO limit global livestock productivity and impact food security and the welfare of domestic animals. This review focusses on implementing previously reviewed diagnostic methods, in a complex epizootiological scenario, by critically assessing diagnostic results at the individual or herd level. In most cases, a single diagnostic method applied at a given time does not unequivocally identify the various parasitological and disease statuses of a host. These include "non-infected", "asymptomatic carrier", "sick infected", "cured/not cured" and/or "multi-infected". The diversity of hosts affected by these animal trypanosomoses and their vectors (or other routes of transmission) is such that integrative, diachronic approaches are needed that combine: (i) parasite detection, (ii) DNA, RNA or antigen detection and (iii) antibody detection, along with epizootiological information. The specificity of antibody detection tests is restricted to the genus or subgenus due to cross-reactivity with other Trypanosoma spp. and Trypanosomatidae, but sensitivity is high. The DNA-based methods implemented over the last three decades have yielded higher specificity and sensitivity for active infection detection in hosts and vectors. However, no single diagnostic

method can detect all active infections and/or trypanosome species or subspecies. The proposed integrative approach will improve the prevention, surveillance and monitoring of animal trypanosomoses with the available diagnostic tools. However, further developments are required to address specific gaps in diagnostic methods and the sustainable control or elimination of these diseases.

Cytotoxic and antiparasitic activities of diphosphine-metal complexes of group 10 containing acylthiourea as ligands.

de Oliveira, T., Ribeiro, G., Honorato, J., Leite, C., Santos, A., Silva, E., Pereira, V., Plutín, A., Cominetti, M., Castellano, E., Batista, A.
20-06-2022
J Inorg Biochem
https://pubmed.ncbi.nlm.nih.gov/35759891

In this work, group 10 transition metal complexes bearing dppe [1,2-bis(diphenylphosphino)ethane] and acylthiourea ligands were evaluated for their cytotoxic and antiparasitic activities. Six new complexes with a general formula $[M(L_n)(dppe)]BF_4$ [where M = Ni^{II}, Pd^{II} or Pt^{II}; L_n = N, N'-dimethyl-N-benzoyl thiourea (L_1) or N, N'-dimethyl-N-tiofenyl thiourea (L_2) were synthesized and characterized by infrared, NMR ($^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$) spectroscopies, elemental analysis and molar conductivity. The structures of the complexes were confirmed by X-ray diffraction technique. The biological activity of the complexes was evaluated on breast cancer cells (MDA-MB-231 and MCF-7) and causative agents of chagas disease and leishmaniasis. The complexes presented higher cytotoxicity for breast cancer cell lines compared to non-tumor cells. Nickel complexes stood out when evaluated against the triple-negative breast cancer line (MDA-MB-231), presenting considerably lower IC_{50} values (about 10 to 22×), when compared to palladium and platinum complexes, and the cisplatin drug. When evaluated on the triple-negative line (MDA-MB-231), the complexes $[Ni(L_2)(dppe)]BF_4$(2), $[Pd(L_2)(dppe)]BF_4$(4) and $[Pt(L_2)(dppe)]BF_4$(6) were able to induce cell morphological changes, influence on the cell colony formation and the size of the cells. The complexes inhibit cell migration and cause changes to the cell cytoskeleton and nuclear arrangement. In the same cell line, the compounds caused cell arrest in the Sub-G1 phase of the cell cycle. The compounds were also tested against the Trypanosom Cruzi (T. cruzi) and Leishmania sp. parasites, which cause Chagas and leishmaniasis disease, respectively. The compounds showed good anti-parasitic activity, mainly for T. cruzi, with lower IC_{50} values, when compared to the commercial drug, benznidazole. The compounds interact with CT-DNA, indicating that interaction occurs by the minor groove of the biomolecule.

Discovery of novel natural products as rhodesain inhibitors for human African trypanosomiasis using in silico techniques.

Elrufaie, H., Mohamed, L., Hamd, A., Bala, N., Elbadawi, F., Ghaboosh, H., Alzain, A.
24-06-2022
J Biomol Struct Dyn
https://doi.org/10.1080/07391102.2022.2092550

Human African Trypanosomiasis (HAT) or sleeping sickness is caused by the *Trypanosoma brucei* rhodesiense, a subspecies of the Trypanosomatide family. The parasite is associated with high morbidity and mortality rate in both animals and humans, claimed to be more fatal than other vector-transmitted diseases such as malaria. The majority of existing medications are highly toxic, not effective in the late chronic phase of the disease, and require maximum dosages to fully eradicate the parasite. In this study, we used computational methods to find out natural products that inhibit the Rhodesain, a parasitic enzyme that plays an important role in the parasite's pathogenicity, multiplication, and ability to pass through the host's blood-brain barrier. A library of 270540 natural products from ZINC databases was processed by using *e*-pharmacophore hypnosis and screening procedures, molecular docking, ADMET processes, and MM-GBSA calculations. This led to the identification of 3 compounds (ZINC000096269390, ZINC000035485292, and ZINC000035485242) which were then subjected to molecular dynamics. The findings of this study showed excellent binding affinity and stability toward the Rhodesain and suggest they may be a hopeful treatment for HAT in the future if further clinical trials were performed.Communicated by Ramaswamy H. Sarma.

Discrete typing units of Trypanosoma cruzi: Geographical and biological distribution in the Americas.

Velásquez-Ortiz, N., Herrera, G., Hernández, C., Muñoz, M., Ramírez, J.
24-06-2022
Sci Data
https://doi.org/10.1038/s41597-022-01452-w

Chagas disease caused by Trypanosoma cruzi is a public health issue in Latin America. This highly diverse parasite is divided into at least seven discrete typing units (DTUs) TcI-TcVI and Tcbat. Some DTUs have been associated with geographical distribution in epidemiological scenarios and clinical manifestations, but these aspects remain poorly understood. Many studies have focused on studying the parasite and its vectors/hosts, using a wide variety of genetic markers and methods. Here, we performed a systematic review of the literature for the last 20 years to present an update of DTUs distribution in the Americas, collecting ecoepidemiological information. We found that the DTUs are widespread across the continent and that there is a whole gamma of genetic markers used for the identification and genotyping of the parasite. The data obtained in this descriptor could improve the molecular epidemiology studies of Chagas disease in endemic regions.

Galectin-3 and fibrosis intensity in Chronic Chagas Cardiomyopathy: a systematic review.

Chaves, A., Oliveira, A., Guimarães, N., Magalhães, I., Menezes, C., Rocha, M.
24-06-2022
Rev Inst Med Trop Sao Paulo
https://pubmed.ncbi.nlm.nih.gov/35749417

Chronic Chagas Cardiomyopathy (CCC) is the most prevalent type of myocarditis and the main clinical form of the Chagas disease, which has peculiarities such as focal inflammation, structural derangement, hypertrophy, dilation, and intense reparative fibrosis. Many cellular compounds contribute to CCC development. Galectin-3 is a partaker in inflammation and contributes to myocardial fibrosis formation. Some studies showed the connection between Galectin-3 and fibrosis in Chagas disease but are still inconclusive on the guidance for the early implementation of pharmacological therapy. This systematic review evaluated Galectin-3 as a biomarker for fibrosis intensity in CCC. Two independent reviewers have searched five databases (PubMed, EMBASE, Cochrane Library, Scopus, and Lilacs), using the following search terms: galectin-3, biomarkers, fibrosis, Chagas cardiomyopathy, and Chagas disease. Overall, seven studies met the inclusion criteria and made up this review. There were four trials conducted through animal model experiments and three trials with humans. Experimental data in mice indicate an association between Galectin-3 expression and fibrosis in CCC (75% of studies). Data from human studies showed no direct connection between myocardial fibrosis and Galectin-3 expression (80% of studies). Thus, human findings do not provide significant evidence indicating that Galectin-3 is related to fibrosis formation in Chagas disease. Based on the analyzed studies, it is suggested that Galectin-3 might not be a good fibrosis marker in CCC.

Health work and skills in the last mile of disease elimination. Experiences from sleeping sickness health workers in South Sudan and DR Congo.

Falisse, J., Mpanya, A., Surur, E., Kingsley, P., Mwamba Miaka, E., Palmer, J.
24-06-2022
Glob Public Health
https://doi.org/10.1080/17441692.2022.2092175

Human African trypanosomiasis (HAT) is considered a highly promising candidate for elimination within the next decade. This paper argues that the experiential knowledge of frontline health workers will be critical to achieve this goal. Interviews are used to explore the ways in which HAT workers understand, maintain, and adjust their skills amidst global and national challenges. We contrast two cases: South Sudan where HAT expertise is scattered and has been repeatedly rebuilt, and the Democratic Republic of Congo (DRC) where specialised mobile detection teams have pro-actively tested people at risk for almost a century. We describe HAT careers where skills are built through participation in HAT technology trials and screening programmes; in the DRC expertise is also supported through formal rotations in screening teams and HAT referral centres for new health workers. As cases fade, de-skilling is a real threat as awareness of populations and authorities diminishes and previously vertical programmes evolve, re-configuring professional development and career paths and associated opportunities for HAT practice. To avoid repeating the mistakes of the 1960s, when elimination also seemed close at hand, we need to recognise that the 'last mile' of elimination hinges on protecting the fragile expertise of frontline health workers.

Preclinical advances and the immunophysiology of a new therapeutic chagas disease vaccine.

Jones, K., Poveda, C., Versteeg, L., Bottazzi, M., Hotez, P.
23-06-2022
Expert Rev Vaccines
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Chronic infection with the protozoal parasite *Trypanosoma cruzi* leads to a progressive cardiac disease, known as chronic Chagasic cardiomyopathy (CCC). A new therapeutic Chagas disease vaccine is in development to augment existing antiparasitic chemotherapy drugs. We report on our current understanding of the underlying immunologic and physiologic mechanisms that lead to CCC, including parasite immune escape mechanisms that allow persistence and the subsequent inflammatory and fibrotic processes that lead to clinical disease. We report on vaccine design and the observed immunotherapeutic effects including induction of a balanced $T_H1/T_H2/T_H17$ immune response that leads to reduced parasite burdens and tissue pathology. Further, we report vaccine-linked chemotherapy, a dose sparing strategy to further reduce parasite burdens and tissue pathology. Our vaccine-linked chemotherapeutic approach is a multimodal treatment strategy, addressing both the parasite persistence and the underlying deleterious host inflammatory and fibrotic responses that lead to cardiac dysfunction. In targeting treatment towards patients with chronic indeterminate or early determinate Chagas disease, this vaccine-linked chemotherapeutic approach will be highly economical and will reduce the global disease burden and deaths due to CCC.

Parasites and blood-meal hosts of the tsetse fly in Tanzania: a metagenomics study.

Kim, J., Choi, J., Nam, S., Fyumagwa, R., Yong, T.
22-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05344-1

Tsetse flies can transmit various Trypanosoma spp. that cause trypanosomiasis in humans, wild animals, and domestic animals. Amplicon deep sequencing of the 12S ribosomal RNA (rRNA) gene can be used to detect mammalian tsetse hosts, and the 18S rRNA gene can be used to detect all associated eukaryotic pathogens, including Trypanosoma spp. Tsetse flies were collected from the Serengeti National Park (n=48), Maswa Game Reserve (n=42), and Tarangire National Park

(n=49) in Tanzania in 2012-13. Amplicon deep sequencing targeting mammal-specific 12S rRNA and 18S rRNA genes was performed to screen the blood-feeding sources of tsetse flies and eukaryotic parasites in tsetse flies, respectively. 12S rRNA gene deep sequencing revealed that various mammals were blood-feeding sources of the tsetse flies, including humans, common warthogs, African buffalos, mice, giraffes, African elephants, waterbucks, and lions. Genes of humans were less frequently detected in Serengeti (P=0.0024), whereas African buffaloes were detected more frequently as a blood-feeding source (P=0.0010). 18S rRNA gene deep sequencing showed that six tsetse samples harbored the Trypanosoma gene, which was identified as Trypanosoma godfreyi and Trypanosoma simiae in subsequent ITS1 gene sequencing. Through amplicon deep sequencing targeting the 12S rRNA and 18S rRNA genes, various mammalian animals were identified as blood-meal sources, and two Trypanosoma species were detected in tsetse flies collected from the Maswa Game Reserve, Serengeti National Park, and Tarangire National Park in Tanzania. This study illustrates the patterns of parasitism of tsetse fly, wild animals targeted by the fly, and Trypanosoma spp. carried by the fly in Tanzania. It may provide essential data for formulating better strategies to control African trypanosomes.

Effects of Structurally Different HDAC Inhibitors against *Trypanosoma cruzi*, *Leishmania*, and *Schistosoma mansoni*.

Di Bello, E., Noce, B., Fioravanti, R., Zwergel, C., Valente, S., Rotili, D., Fianco, G., Trisciuoglio, D., Mourão, M., Sales, P., Lamotte, S., Prina, E., Späth, G., Häberli, C., Keiser, J., Mai, A.
22-06-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.2c00232

Neglected tropical diseases (NTDs), including trypanosomiasis, leishmaniasis, and schistosomiasis, result in a significant burden in terms of morbidity and mortality worldwide every year. Current antiparasitic drugs suffer from several limitations such as toxicity, no efficacy toward all of the forms of the parasites' life cycle, and/or induction of resistance. Histone-modifying enzymes play a crucial role in parasite growth and survival; thus, the use of epigenetic drugs has been suggested as a strategy for the treatment of NTDs. We tested structurally different HDACi **1**-**9**, chosen from our in-house library or newly synthesized, against *Trypanosoma cruzi, Leishmania* spp, and *Schistosoma mansoni*. Among them, **4** emerged as the most potent against all of the tested parasites, but it was too toxic against host cells, hampering further studies. The retinoic 2'-aminoanilide **8** was less potent than **4** in all parasitic assays, but as its toxicity is considerably lower, it could be the starting structure for further development. In *T. cruzi*, compound **3** exhibited a single-digit micromolar inhibition of parasite growth combined with moderate toxicity. In *S. mansoni*, **4**'s close analogs **17**-**20** were tested in new transformed schistosomula (NTS) and adult worms displaying high death induction against both parasite forms. Among them, **17** and **19** exhibited very low toxicity in human retinal pigment epithelial (RPE) cells, thus being promising compounds for further optimization.

Myocardial Injury in Patients With Acute and Subacute Chagas Disease in the Brazilian Amazon Using Cardiovascular Magnetic Resonance.

Couceiro, K., Ortiz, J., Hosannah da Silva E Silva, M., Teixeira de Sousa, D., Andrade, R., Brandão, A., de Morais, R., Smith Doria, S., Fonseca, R., da Silva, P., Fernandes, F., Guerra, M., Rochitte, C., Ferreira, J., Guerra, J.
22-06-2022
J Am Heart Assoc
https://doi.org/10.1161/JAHA.121.021806

Background Chagas disease is a neglected tropical disease that is still considered a global health emergency. In the Amazon region, most of the reports are of acute cases that are associated with oral transmission. This study aimed to evaluate myocardial injury in patients with acute Chagas disease before and after treatment. Methods and Results We evaluated 23 patients with acute Chagas disease in 3 different stages of progression. Group 1 had 12 patients evaluated during the acute phase, at the time of diagnosis, and 1 year after treatment, and Group 2 had 11 patients in the late postacute phase who were evaluated 5.2 years on average after diagnosis and treatment. ECGs with the Selvester score, 24-hour Holter exam, and cardiovascular magnetic resonance imaging were performed. The mean age of the 23 patients was 44.3±18.9 years, and they were mostly men (15/65.24%) from Amazonas state (22/95.6%). In 69.6% (n=16) of the patients, some ECG alterations were found, the most frequent being left anterior fascicular block and ventricular repolarization. In Group 1, the 24-hour Holter exam showed atrial tachycardia in 3 (25%) patients and ventricular extrasystoles in 2 (16.7%) patients. In Group 2, 1 patient had ventricular extrasystoles. Myocardial injury was observed in 7 patients (58.3%) at the acute phase and in 5 (50%) patients at the 1-year follow-up in Group 1 and in 2 (18.2%) patients in Group 2. Conclusions This article describes, for the first time, myocardial injury shown by cardiovascular magnetic resonance imaging in a group of patients with acute Chagas disease and reveals the importance of early detection and follow-up of the cardiac impairment in these patients.

LEISHMANIOSE

Cell-intrinsic Wnt4 ligand regulates mitochondrial oxidative phosphorylation in macrophages.

Tlili, M., Acevedo, H., Descoteaux, A., Germain, M., Heinonen, K.
25-06-2022
J Biol Chem
https://pubmed.ncbi.nlm.nih.gov/35764169

Macrophages respond to their environment by adopting a predominantly inflammatory or anti-inflammatory profile, depending on the context. The polarization of the subsequent response is regulated by a combination of intrinsic and extrinsic signals and is associated with alterations in macrophage metabolism. Although macrophages are important producers of Wnt ligands, the role of Wnt signaling in regulating metabolic changes associated with macrophage polarization remains unclear. Wnt4 upregulation has been shown to be associated with tissue repair and suppression of age-associated inflammation, which led us to generate Wnt4-deficient bone marrow-derived macrophages (BMDMs) to investigate its role in metabolism. We show that loss of Wnt4 led to modified mitochondrial structure, enhanced oxidative phosphorylation, and depleted intracellular lipid reserves, as the cells depended on fatty acid oxidation to fuel their mitochondria. Further we found that enhanced lipolysis was dependent on protein kinase C (PKC)-mediated activation of lysosomal acid lipase in Wnt4-deficient BMDMs. Although not irreversible, these metabolic changes promoted parasite survival during infection with Leishmania donovani. In conclusion, our results indicate that enhanced macrophage fatty acid oxidation impairs the control of intracellular pathogens, such as Leishmania. We further suggest that Wnt4 may represent a potential target in atherosclerosis, which is characterized by lipid storage in macrophages leading to them becoming foam cells.

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry: An effective method for identification and phylogenetic analysis of Leishmania species.

Kuang, Z., Zhang, C., Meng, Y., Yi, F., Ma, Y.
25-06-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35764122

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a rapid and reproducible method that has been widely applied for the identification of bacteria and fungi. However, this technique has not yet been applied in clinical laboratories for parasitology, such as for the study of the protozoan Leishmania. By using MALDI-TOF MS, mass spectra database entries (MSPs) were created with 7 World Health Organization reference strains in order to establish a rapid method for Leishmania species identification. Furthermore, cluster analysis was performed with 18 Chinese Leishmania isolates. The MSPs of Leishmania corresponded well with our past identification results, and the dendrogram analysis result was more or less similar to that of the phylogenetic analysis performed by multi-locus sequence typing. MALDI-TOF MS is a promising method that offers both rapidity and efficiency for the identification and dendrogram analysis of Leishmania species.

The host micro-RNA cfa-miR-346 is induced in canine leishmaniasis.

Buffi, G., Diotallevi, A., Ceccarelli, M., Bruno, F., Castelli, G., Vitale, F., Magnani, M., Galluzzi, L.
27-06-2022
BMC Vet Res
https://doi.org/10.1186/s12917-022-03359-5

Leishmaniases are a group of anthropo-zoonotic parasitic diseases caused by a protozoan of the Leishmania genus, affecting both humans and other vertebrates, including dogs. L. infantum is responsible for the visceral and occasionally cutaneous form of the disease in humans and canine leishmaniasis. Previously, we have shown that L. infantum induces a mild but significant increase in endoplasmic reticulum (ER) stress expression markers to promote parasites survival in human and murine infected macrophages. Moreover, we demonstrated that the miRNA hsa-miR-346, induced by the UPR-activated transcription factor sXBP1, was significantly upregulated in human macrophages infected with different L. infantum strains. However, the ER stress response in infected dogs, which represent an important reservoir for Leishmania parasite, was described once recently, whereas the miR-346 expression was not reported before. Therefore, this study aimed to investigate these pathways in the canine macrophage-like cell line DH82 infected by Leishmania spp. and to evaluate the presence of cfa-miR-346 in plasma of non-infected and infected dogs. The DH82 cells were infected with L. infantum and L. braziliensis parasites and the expression of cfa-mir-346 and several ER stress markers was evaluated by quantitative PCR (qPCR) at different time points. Furthermore, the cfa-miR-346 was monitored in plasma collected from non-infected dogs (n=11) and dogs naturally infected by L. infantum (n=18). The results in DH82 cells showed that cfa-mir-346 was induced at both 24 h and 48 h post-infection with all Leishmania strains but not with tunicamycin, accounting for a mechanism of induction independent from sXBP1, unlike what was previously observed in human cell lines. Moreover, the cfa-miR-346 expression analysis on plasma revealed a significant increase in infected dogs compared to non-infected dogs. Here for the first time, we report the upregulation of cfa-miR-346 induced by Leishmania infection in canine macrophage-like cells and plasma samples of naturally infected dogs. According to our results, the cfa-miR-346 appears to be linked to infection, and understanding its role and identifying its target genes could contribute to elucidate the mechanisms underlying the host-pathogen interaction in leishmaniasis.

Cytotoxic and antiparasitic activities of diphosphine-metal complexes of group 10 containing acylthiourea as ligands.

de Oliveira, T., Ribeiro, G., Honorato, J., Leite, C., Santos, A., Silva, E., Pereira, V., Plutín, A., Cominetti, M., Castellano, E., Batista, A.
20-06-2022
J Inorg Biochem
https://pubmed.ncbi.nlm.nih.gov/35759891

In this work, group 10 transition metal complexes bearing dppe [1,2-bis(diphenylphosphino)ethane] and acylthiourea ligands were evaluated for their cytotoxic and antiparasitic activities. Six new complexes with a general formula $[M(L_n)(dppe)]BF_4$ [where M = Ni^{II}, Pd^{II} or Pt^{II}; L_n = N, N'-dimethyl-N-benzoyl thiourea (L_1) or N, N'-dimethyl-N-tiofenyl thiourea (L_2) were synthesized and characterized by infrared, NMR ($^{31}P\{^1H\}$, ^1H and $^{13}C\{^1H\}$) spectroscopies, elemental analysis and molar conductivity. The structures of the complexes were confirmed by X-ray diffraction technique. The biological activity of the complexes was evaluated on breast cancer cells (MDA-MB-231 and MCF-7) and causative agents of chagas disease and leishmaniasis. The complexes presented higher cytotoxicity for breast cancer cell lines compared to non-tumor cells. Nickel complexes stood out when evaluated against the triple-negative breast cancer line (MDA-MB-231), presenting considerably lower IC_{50} values (about 10 to 22×), when compared to palladium and platinum complexes, and the cisplatin drug. When evaluated on the triple-negative line (MDA-MB-231), the complexes $[Ni(L_2)(dppe)]BF_4$(2), $[Pd(L_2)(dppe)]BF_4$(4) and $[Pt(L_2)(dppe)]BF_4$(6) were able to induce cell morphological changes, influence on the cell colony formation and the size of the cells. The complexes inhibit cell migration and cause changes to the cell cytoskeleton and nuclear arrangement. In the same cell line, the compounds caused cell arrest in the Sub-G1 phase of the cell cycle. The compounds were also tested against the Trypanosom Cruzi (T. cruzi) and Leishmania sp. parasites, which cause Chagas and leishmaniasis disease, respectively. The compounds showed good anti-parasitic activity, mainly for T. cruzi, with lower IC_{50} values, when compared to the commercial drug, benznidazole. The compounds interact with CT-DNA, indicating that interaction occurs by the minor groove of the biomolecule.

Development of an immunogen containing $CD4^+/CD8^+$ T-cell epitopes for the prophylaxis of tegumentary leishmaniasis.

de Andrade Ferraz, I., Carvalho, A., de Brito, R., Roatt, B., Martins, V., Lage, D., Dos Reis Cruz, L., Medeiros, F., Gonçalves, D., da Costa Rocha, M., Coelho, E., de Oliveira Mendes, T., Duarte, M., Menezes-Souza, D.
27-06-2022
Appl Microbiol Biotechnol
https://doi.org/10.1007/s00253-022-12033-7

Tegumentary leishmaniasis (TL) is a disease of high severity and incidence in Brazil, and Leishmania braziliensis is its main etiological agent. The inefficiency of control measures, such as high toxicity and costs of current treatments and the lack of effective immunoprophylactic strategies, makes the development of vaccines indispensable and imminent. In this light, the present work developed a gene encoding multiple T-cell ($CD4^+/CD8^+$) epitope, derived from conserved proteins found in Leishmania species and associated with TL, to generate a chimeric protein (rMEP/TL) and compose a vaccine formulation. For this, six T-cell epitopes were selected by immunoinformatics approaches from proteins present in the amastigote stage and associated with host-parasite interactions. The following formulations were then tested in an L. braziliensis murine infection model: rMEP/TL in saline or associated with MPLA-PHAD®. Our data revealed that, after immunization (three doses; 14-day intervals) and subsequent challenging, rMEP/TL and rMEP/TL+MPLA-vaccinated mice showed an increased production of key immunological biomarkers of protection, such as IgG_{2a}, IgG_{2a}/IgG_1, NO, $CD4^+$, and $CD8^+$ T-cells with IFN-γ and TNF-α production, associated with a reduction in $CD4^+IL\text{-}10^+$ and $CD8^+IL\text{-}10^+$ T-cells. Vaccines also induced the development of central ($CD44^{high}CD62L^{high}$) and effector ($CD44^{high}CD62L^{low}$) memory of $CD4^+$ and $CD8^+$ T-cells. These findings, associated with the observation of lower rates of parasite burdens in the vaccinated groups, when compared to the control groups, suggest that immunization with rMEP/TL and, preferably, associated with an adjuvant, may be considered an effective tool to prevent TL. KEY POINTS: • Rational design approaches for vaccine development. • Central and effector memory of CD4+ and CD8+ T-cells. • Vaccine comprised of rMEP/TL plus MPLA as an effective tool to prevent TL.

DEFINITION OF THE MAIN VECTOR OF CUTANEOUS LEISHMANIASIS: ECOLOGY AND MAPPING IN ENDEMIC AREA OF NORTHEAST BRAZIL.

Araújo, A., Ebbers, W., Feitosa, A., Silva, D., Bandeira, R., Velásquez, C., Pessoa, F., Alves, L., Brayner, F.
23-06-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35753387

Cutaneous leishmaniasis is endemic in Pernambuco. Aiming to determine the vector species of cutaneous leishmaniasis in an endemic area of the Northeast region of Brazil, this study aimed to use the spatial mapping of human cases of CL and correlate with ecological studies of the vectors in the municipality of Timbaúba, Pernambuco, Brazil. Individuals infected with CL were recruited through active search in their homes and clinically and serologically diagnosed during the period from 2018 to 2019. Sandflies were captured with CDC-type light traps in peridomiciliary environments and these were identified at the species level. Females were separated for DNA extraction and subsequent analysis by PCR. The points of collection of phlebotomes and the residences of individuals with lesions were marked with GPS. During the study period, 60 cases of CL were diagnosed. A higher concentration of CL cases was observed in proximity to Atlantic forest remnants confirmed by heat map. A total of 3,744 sandflies was captured and five distinct species were identified, with the predominance of Nyssomyia whitmani. From the females separated for the identification of Leishmania braziliensis DNA, a rate of 0.68% of infected sandflies was obtained. It was concluded that cutaneous leishmaniasis continues to be a rural feature of the area. And from this study, it is concluded that Ny. whitmani is the carrier species of CL in the municipality of Timbaúba, Pernambuco. This is due to abundance in catching, specialization of species and PCR positivity for Leishmania braziliensis.

Long-term hematopoietic stem cells as a parasite niche during treatment failure in visceral leishmaniasis.

Dirkx, L., Hendrickx, S., Merlot, M., Bulté, D., Starick, M., Elst, J., Bafica, A., Ebo, D., Maes, L., Van Weyenbergh, J., Caljon, G.
25-06-2022
Commun Biol
https://doi.org/10.1038/s42003-022-03591-7

Given the discontinuation of various first-line drugs for visceral leishmaniasis (VL), large-scale in vivo drug screening, establishment of a relapse model in rodents, immunophenotyping, and transcriptomics were combined to study persistent infections and therapeutic failure. Double bioluminescent/fluorescent Leishmania infantum and L. donovani reporter lines enabled the identification of long-term hematopoietic stem cells (LT-HSC) as a niche in the bone marrow with remarkably high parasite burdens, a feature confirmed for human hematopoietic stem cells (hHSPC). LT-HSC are more tolerant to antileishmanial drug action and serve as source of relapse. A unique transcriptional 'StemLeish' signature in these cells was defined by upregulated TNF/NF-κB and RGS1/TGF-β/SMAD/SKIL signaling, and a downregulated oxidative burst. Cross-species analyses demonstrated significant overlap with human VL and HIV co-infected blood transcriptomes. In summary, the identification of LT-HSC as a drug- and oxidative stress-resistant niche, undergoing a conserved transcriptional reprogramming underlying Leishmania persistence and treatment failure, may open therapeutic avenues for leishmaniasis.

Wild micromammal host spectrum of zoonotic eukaryotic parasites in Spain. Occurrence and genetic characterization.

Vioque, F., Dashti, A., Santín, M., Ruiz-Fons, F., Köster, P., Hernández-Castro, C., García, J., Bailo, B., Ortega, S., Olea, P., Arce, F., Chicharro, C., Nieto, J., González, F., Viñuela, J., Carmena, D., González-Barrio, D.
25-06-2022
Transbound Emerg Dis
https://doi.org/10.1111/tbed.14643

Micromammals have historically been recognized as highly contentious species in terms of maintenance and transmission of zoonotic pathogens to humans. Limited information is currently available on the epidemiology and potential public health significance of intestinal eukaryotes in wild micromammals. We examined 490 faecal samples, grouped in 155 pools, obtained from 11 micromammal species captured in 11 Spanish provinces for the presence of DNA from Cryptosporidium spp., Giardia duodenalis, Enterocytozoon bieneusi, and Blastocystis sp. The presence of Leishmania spp. was investigated in individual spleen samples. All micromammal species investigated harboured infections by at least one eukaryotic parasite, except Apodemus flavicollis, Myodes glareolus, Sorex coronatus and Sciurus vulgaris, but sample size for these host species was very low. Cryptosporidium spp. was the most prevalent species found (3.7%, 95% CI: 2.2-5.7), followed by G. duodenalis (2.8%, 95% CI: 1.6-4.6) and E. bieneusi (2.6%, 95% CI: 1.4-4.3). All pooled faecal samples tested negative for Blastocystis sp. Leishmania infantum was identified in 0.41% (95% CI: 0.05-1.46) of the 490 individual spleen samples analysed. Sequences analyses allowed the identification of C. andersoni (5.9%), C. ditrichi (11.7%), C. muris (5.9%), C. parvum (5.9%), C. tyzzeri (5.9%), rat genotypes CR97 (5.9%) and W19 (5.9%), vole genotypes V (11.7%) and VII (5.9%) and Cryptosproridium spp. (35.3%) within Cryptosporidium (n = 17). Known genotypes C (66.7%) and Peru11 (25.0%), and a novel genotype (named MouseSpEb1, 8.3%) were detected within E. bieneusi (n = 12). None of the G. duodenalis-positive samples could be genotyped at the assemblage level. Molecular data indicate that wild micromammals were primarily infected by rodent-adapted species/genotypes of eukaryotic pathogens and thereby have a limited role as source of human infections. The presence of ruminant-adapted species C. andersoni along with finding C. parvum is indicative of an overlap between domestic/peri-domestic and sylvatic transmission cycles of these agents.

Geographic distribution of human leishmaniasis and phlebotomine sand flies in the State of Mato Grosso do Sul, Brazil.

Neitzke-Abreu, H., Costa, G., da Silva, M., Palacio, E., da Silva Cardoso, A., de Almeida, P., da Costa Lima-Junior, M.
24-06-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05353-0

In the State of Mato Grosso do Sul, Brazil, sand flies and cases of visceral (VL) and cutaneous (CL) leishmaniases have been reported in almost all municipalities. The aim of this study was to analyze the geographic distribution of VL and CL in relation the sand fly species found in the municipalities of Mato Grosso do Sul. We analyzed VL and CL cases from 2001 to 2018 using data from the Notifiable Diseases Information System (SINAN). Data collected since 2003 on the presence of sand fly vectors (proven or suspected) were provided by the State Health Secretariat. A total of 3566 and 3030 cases of VL and CL, respectively, were reported from 2001 to 2018. The municipalities with the most reported cases of VL were Campo Grande (2495), Três Lagoas (442), Corumbá (140) and Aquidauana (136); and those for CL were Campo Grande (635) and Bodoquena (197). The following sand fly species with vector potential were found in 59 municipalities (74.7%): Lutzomyia longipalpis, Lutzomyia cruzi, Nyssomyia whitmani, Migonemyia migonei, Nyssomyia neivai, Pintomyia pessoai, Bichromomyia flaviscutellata and Pintomyia fischeri. Sand flies were present in six municipalities where no cases of VL were reported and in two municipalities where no cases of CL were reported. Our results indicate that the geographical distribution of VL and CL in Mato Grosso do Sul expanded during the study period, and highlight the presence of sand fly vectors in municipalities where these diseases are currently considered to be non-endemic.

Genotypic and phylogenic analyses of cutaneous leishmaniasis in Al Ahsa, Eastern Saudi Arabia during the coronavirus disease 2019 pandemic: First cases of Leishmania tropica with the predominance of Leishmania major.

Al-Rashed, A., Al Jindan, R., Al Jaroodi, S., Al Mohanna, A., Abdelhady, A., El-Badry, A.
24-06-2022
Sci Rep
https://doi.org/10.1038/s41598-022-14702-z

During the coronavirus disease 2019 lockdown period, a surge in sandflies and cutaneous leishmaniasis (CL) cases was observed in Al-Ahsa, Saudi Arabia. Skin punch biopsies were obtained from 100 patients clinically diagnosed with CL in Al-Ahsa who had no travel history in the last 6 months. Impression smears were used following a three-step polymerase chain reaction (PCR) protocol using genus-specific primers targeting kDNA and ITS1. Leishmania speciation was determined by ITS1 PCR/nested PCR-restriction fragment length polymorphism and sequencing. A phylogenetic tree was constructed. The associated patient characteristics were analyzed. Using internal transcribed spacer one (ITS1)-PCR/nested PCR, 98 cases were considered true-positive CL. Leishmania major was the predominant species, and Leishmania tropica was identified in three cases. Microscopy had poor sensitivity and perfect specificity. Direct ITS1-PCR missed nine cases. Sex, residence, and treatment outcome were significantly associated with the occurrence of Leishmania; distribution of skin lesion(s) and treatment outcome were significantly associated with Leishmania genotype. This is the first time that L. tropica was identified as a cause of CL in human in Al-Ahsa, in addition to the predominant zoonotic species, L. major. We recommend using ITS1-nested PCR for negative cases by ITS1-PCR. Further exploration of Leishmania transmission dynamics in vectors and reservoir animals is essential for designing effective preventive measures.

Antiprotozoal activity of different Xenorhabdus and Photorhabdus bacterial secondary metabolites and identification of bioactive compounds using the easyPACId approach.

Gulsen, S., Tileklioglu, E., Bode, E., Cimen, H., Ertabaklar, H., Ulug, D., Ertug, S., Wenski, S., Touray, M., Hazir, C., Bilecenoglu, D., Yildiz, I., Bode, H., Hazir, S.
24-06-2022
Sci Rep
https://doi.org/10.1038/s41598-022-13722-z

Natural products have been proven to be important starting points for the development of new drugs. Bacteria in the genera Photorhabdus and Xenorhabdus produce antimicrobial compounds as secondary metabolites to compete with other organisms. Our study is the first comprehensive study screening the anti-protozoal activity of supernatants containing secondary metabolites produced by 5 Photorhabdus and 22 Xenorhabdus species against human parasitic protozoa, Acanthamoeba castellanii, Entamoeba histolytica, Trichomonas vaginalis, Leishmania tropica and Trypanosoma cruzi, and the identification of novel bioactive antiprotozoal compounds using the easyPACId approach (easy Promoter Activated Compound Identification) method. Though not in all species, both bacterial genera produce antiprotozoal compounds effective on human pathogenic protozoa. The promoter exchange mutants revealed that antiprotozoal bioactive compounds produced by Xenorhabdus bacteria were fabclavines, xenocoumacins, xenorhabdins and PAX peptides. Among the bacteria assessed, only P. namnaoensis appears to have acquired amoebicidal property which is effective on E. histolytica trophozoites. These discovered antiprotozoal compounds might serve as starting points for the development of alternative and novel pharmaceutical agents against human parasitic protozoa in the future.

Artificial intelligence channelizing protein-peptide interactions pipeline for host-parasite paradigm in IL-10 and IL-12 reciprocity by SHP-1.

Khandibharad, S., Singh, S.
21-06-2022
Biochim Biophys Acta Mol Basis Dis
https://pubmed.ncbi.nlm.nih.gov/35750267

Identification of molecular targets in any cellular phenomena is a challenge and a path that one endeavors upon independently. We have identified a phosphatase SHP-1 as a point of intervention of IL-10 and IL-12 reciprocity in leishmaniasis. The therapeutic model that we have developed uniquely targets this protein but the pipeline in general can be used by the researchers for their unique targets. Naturally occurring peptides are well known for their biochemical participation in cellular functions hence we were motivated to use this uniqueness of physico-chemical properties of peptides conferred by amino acids through machine learning to channelize a mode of therapeutic exploration in infectious disease. Using computational approaches, we identified high order sequence conservation and similarity in SHP-1 sequence which was also evolutionarily conserved, complete structure of Mouse SHP-1 was predicted and validated, a unique motif of the same was identified against which library of synthetic peptides were designed and validated followed by screening the library by docking them with MuSHP-1 protein structure. Our findings showed 3 peptides had high binding affinity and in future can be validated using cell based and in vivo assays.

Impaired in vitro Interferon-γ production in patients with visceral leishmaniasis is improved by inhibition of PD1/PDL-1 ligation.

Takele, Y., Adem, E., Franssen, S., Womersley, R., Kaforou, M., Levin, M., Müller, I., Cotton, J., Kropf, P.
24-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010544

Visceral leishmaniasis (VL) is a neglected tropical disease that

causes substantial morbidity and mortality and is a growing health problem in Ethiopia, where this study took place. Most individuals infected with Leishmania donovani parasites will stay asymptomatic, but some develop VL that, if left untreated, is almost always fatal. This stage of the disease is associated with a profound immunosuppression, characterised by impaired production of Interferonγ (IFNγ), a cytokine that plays a key role in the control of Leishmania parasites, and high expression levels of an inhibitory receptor, programmed cell death 1 (PD1) on CD4+ T cells. Here, we tested the contribution of the interaction between the immune checkpoint PD1 and its ligand PDL-1 on the impaired production of IFNγ in VL patients. Our results show that in the blood of VL patients, not only CD4+, but also CD8+ T cells express high levels of PD1 at the time of VL diagnosis. Next, we identified PDL-1 expression on different monocyte subsets and neutrophils and show that PDL-1 levels were significantly increased in VL patients. PD1/PDL-1 inhibition resulted in significantly increased production of IFNγ, suggesting that therapy using immune checkpoint inhibitors might improve disease control in these patients.

Leishmania guyanensis M4147 as a new LRV1-bearing model parasite: Phosphatidate phosphatase 2-like protein controls cell cycle progression and intracellular lipid content.

Zakharova, A., Albanaz, A., Opperdoes, F., Škodová-Sveráková, I., Zagirova, D., Saura, A., Chmelová, L., Gerasimov, E., Leštinová, T., Bečvář, T., Sádlová, J., Volf, P., Lukeš, J., Horváth, A., Butenko, A., Yurchenko, V.
24-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010510

Leishmaniasis is a parasitic vector-borne disease caused by the protistan flagellates of the genus Leishmania. Leishmania (Viannia) guyanensis is one of the most common causative agents of the American tegumentary leishmaniasis. It has previously been shown that L. guyanensis strains that carry the endosymbiotic Leishmania RNA virus 1 (LRV1) cause more severe form of the disease in a mouse model than those that do not. The presence of the virus was implicated into the parasite's replication and spreading. In this respect, studying the molecular mechanisms of cellular control of viral infection is of great medical importance. Here, we report ~30.5 Mb high-quality genome assembly of the LRV1-positive L. guyanensis M4147. This strain was turned into a model by establishing the CRISPR-Cas9 system and ablating the gene encoding phosphatidate phosphatase 2-like (PAP2L) protein. The orthologue of this gene is conspicuously absent from the genome of an unusual member of the family Trypanosomatidae, Vickermania ingenoplastis, a species with mostly bi-flagellated cells. Our analysis of the PAP2L-null L. guyanensis showed an increase in the number of cells strikingly resembling the bi-flagellated V. ingenoplastis, likely as a result of the disruption of the cell cycle, significant accumulation of phosphatidic acid, and increased virulence compared to the wild type cells.

Refractory esophagitis caused by *Candida nivariensis*: second description of this yeast in Brazil and a literature review.

Sousa, B., Freitas, J., Valeriano, C., Neto, L., Neves, R., Gambarra, F., Gomes, T., da Silva Acioly, J., Lima-Neto, R.
24-06-2022
Future Microbiol
https://doi.org/10.2217/fmb-2021-0109

Candida nivariensis caused refractory esophagitis in a 36-year-old Brazilian man coinfected with HIV and *Leishmania*. A literature review on this rare fungal pathogen is also presented. The diagnosis was made, and pathogen identification was performed using matrix-assisted laser desorption ionization-time of flight mass spectrometry and sequencing of the *LSU/26S* region. An antifungigram was performed using broth microdilution. A literature search of PubMed was performed. The causative agent, *C. nivariensis*, was resistant to fluconazole and voriconazole. The patient's condition worsened considerably, and he passed away. This is the second report of this *Candida* species in Brazil and the first case reported worldwide of refractory esophagitis in a patient coinfected with HIV and *Leishmania*. The case illustrates the importance of precise identification and antifungal susceptibility testing when isolating this emerging pathogen.

Immunotherapy for visceral leishmaniasis: A trapeze of balancing counteractive forces.

Revue de littérature

Mazire, P., Saha, B., Roy, A.
20-06-2022
Int Immunopharmacol
https://pubmed.ncbi.nlm.nih.gov/35738089

The protozoan parasite Leishmania donovani, residing and replicating within the cells of the monocyte-macrophage (mono-mac) lineage, causes visceral leishmaniasis (VL) in humans. While, Leishmania infantum, is the main causative agent for zoonotic VL, where dogs are the main reservoirs of the disease. The chemotherapy is a serious problem because of restricted repertoire of drugs, drug-resistant parasites, drug-toxicity and the requirement for parenteral administration, which is a problem in resource-starved countries. Moreover, immunocompromised individuals, particularly HIV-1 infected are at higher risk of VL due to impairment in T-helper cell and regulatory cell responses. Furthermore, HIV-VL co-infected patients report poor response to conventional chemotherapy. Recent efforts are therefore directed towards devising both prophylactic and therapeutic immunomodulation. As far as prophylaxis is concerned, although canine vaccines for the disease caused by Leishmania infantum or Leishmania chagasi are available, no vaccine is available for use in humans till date. Therefore, anti-leishmanial immunotherapy triggering or manipulating the host's immune response is gaining momentum during the last two decades. Immunomodulators comprised of small molecules, anti-leishmanial peptides, complex ligands for host receptors, cytokines or their agonists and antibodies have

been given trials both in experimental models and in humans. However, the success of immunotherapy in humans remains a far-off target. We, therefore, propose that devising a successful immunotherapy is an act of balancing enhanced beneficial Leishmania-specific responses and deleterious immune activation/hyperinflammation just as the swings in a trapeze.

Canine Cytokines Profile in an Endemic Region of *L. infantum*: Related Factors.

Marín-García, P., Llobat, L.
20-06-2022
Vet Sci
https://pubmed.ncbi.nlm.nih.gov/35737357

Canine leishmaniosis is caused by infection with parasite *Leishmania infantum*, which are transmitted by sandflies *Phlebotomus.* Canine leishmaniosis is an endemic disease in the Mediterranean region. The immune response could vary between hosts and determines the severity of the disease and clinical features. The aim of this study was to analyze the serum levels of cytokines TNF-α, IFN-γ, IL-2, IL-6, and IL-8, which are related to the activation of Th1 or Th2 immune responses in dogs living in the *L. infantum* endemic region. Moreover, we intend to relate and correlate these levels with different factors, such as sex, age, diet, lifestyle, and breed. Epidemiological data and serum were recovered for seventy-eight dogs, and serum levels of cytokines described previously were analyzed by using the ELISA method. The results showed differences in serum levels of IFN-γ, IL-2, and IL-8 between breeds. The lifestyle also affected serum levels of IL-2. The main conclusion of this study is that Ibizan hounds and crossbred dogs have a serological profile of cytokines that seems to indicate certain protections against infection by *L. infantum* compared to boxer and purebred breeds.

The Natural Alkaloid Tryptanthrin Induces Apoptosis-like Death in *Leishmania* spp.

Garcia, A., Silva-Luiz, Y., Alviano, C., Alviano, D., Vermelho, A., Rodrigues, I.
20-06-2022
Trop Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35736990

Leishmaniasis is a vector-borne disease against which there are no approved vaccines, and the treatment is based on highly toxic drugs. The alkaloids consist of a chemical class of natural nitrogen-containing substances with a long history of antileishmanial activity. The present study aimed at determining the antileishmanial activity and in silico pharmacokinetic and toxicological potentials of tryptanthrin alkaloid. The anti-*Leishmania amazonensis* and anti-*L. infantum* assays were performed against both promastigotes and intracellular amastigotes. Cellular viability was determined by parasites' ability to grow (promastigotes) or differentiate (amastigotes) after incubation with tryptanthrin. The mechanisms of action were explored by mitochondrion dysfunction and apoptosis-like death evaluation. For the computational pharmacokinetics and toxicological analysis (ADMET), tryptanthrin was submitted to the PreADMET webserver. The alkaloid displayed anti-promastigote activity against *L. amazonensis* and *L. infantum* (IC_{50} = 11 and 8.0 µM, respectively). Tryptanthrin was active against intracellular amastigotes with IC_{50} values of 75 and 115 µM, respectively. Mitochondrial membrane depolarization was observed in tryptanthrin-treated promastigotes. In addition, parasites undergoing apoptosis-like death were detected after 18 h of exposure. In silico ADMET predictions revealed that tryptanthrin has pharmacokinetic and toxicological properties similar to miltefosine. The results presented herein demonstrate that tryptanthrin is an interesting drug candidate against leishmaniasis.

Visceral leishmaniasis: an unusual cause of isolated lymphadenopathy.

Palmic, P., Blanche, P., Bouscary, D., Birsen, R.
22-06-2022
BMJ Case Rep
https://pubmed.ncbi.nlm.nih.gov/35732374

Effects of Structurally Different HDAC Inhibitors against *Trypanosoma cruzi*, *Leishmania*, and *Schistosoma mansoni*.

Di Bello, E., Noce, B., Fioravanti, R., Zwergel, C., Valente, S., Rotili, D., Fianco, G., Trisciuoglio, D., Mourão, M., Sales, P., Lamotte, S., Prina, E., Späth, G., Häberli, C., Keiser, J., Mai, A.
22-06-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.2c00232

Neglected tropical diseases (NTDs), including trypanosomiasis, leishmaniasis, and schistosomiasis, result in a significant burden in terms of morbidity and mortality worldwide every year. Current antiparasitic drugs suffer from several limitations such as toxicity, no efficacy toward all of the forms of the parasites' life cycle, and/or induction of resistance. Histone-modifying enzymes play a crucial role in parasite growth and survival; thus, the use of epigenetic drugs has been suggested as a strategy for the treatment of NTDs. We tested structurally different HDACi **1**-**9**, chosen from our in-house library or newly synthesized, against *Trypanosoma cruzi, Leishmania* spp, and *Schistosoma mansoni*. Among them, **4** emerged as the most potent against all of the tested parasites, but it was too toxic against host cells, hampering further studies. The retinoic 2'-aminoanilide **8** was less potent than **4** in all parasitic assays, but as its toxicity is considerably lower, it could be the starting structure for further development. In *T. cruzi*, compound **3** exhibited a single-digit micromolar inhibition of parasite growth combined with moderate toxicity. In *S. mansoni*, **4**'s close analogs **17**-**20** were tested in new transformed schistosomula (NTS) and adult worms displaying high death induction against both parasite forms. Among them, **17** and **19** exhibited very low toxicity in human retinal pigment epithelial (RPE) cells, thus being promising compounds for further optimization.

Essential Role of Enzymatic Activity in the Leishmanicidal Mechanism of the Eosinophil Cationic Protein (RNase 3).

Abengózar, M., Fernández-Reyes, M., Salazar, V., Torrent, M., de la Torre, B., Andreu, D., Boix, E., Rivas, L.
22-06-2022
ACS Infect Dis
https://doi.org/10.1021/acsinfecdis.1c00537

The recruitment of eosinophils into *Leishmania* lesions is frequently associated with a favorable evolution. A feasible effector for this process is eosinophil cationic protein (ECP, RNase 3), one of the main human eosinophil granule proteins, endowed with a broad spectrum of antimicrobial activity, including parasites. ECP was active on *Leishmania* promastigotes and axenic amastigotes (LC_{50}'s = 3 and 16 µM, respectively) but, in contrast to the irreversible membrane damage caused on bacteria and reproduced by its *N*-terminal peptides, it only induced a mild and transient plasma membrane destabilization on *Leishmania donovani* promastigotes. To assess the contribution of RNase activity to the overall leishmanicidal activity of ECP, parasites were challenged in parallel with a single-mutant version, ECP-H15A, devoid of RNase activity, that fully preserves the conformation and liposome permeabilization ability. ECP-H15A showed a similar uptake to ECP on promastigotes, but with higher LC_{50}'s (>25 µM) for both parasite stages. ECP-treated promastigotes showed a degraded RNA pattern, absent in ECP-H15A-treated samples. Moreover ECP, but not ECP-H15A, reduced more than 2-fold the parasite burden of infected macrophages. Altogether, our results suggest that ECP enters the *Leishmania* cytoplasm by an endocytic pathway, ultimately leading to RNA degradation as a key contribution to the leishmanicidal mechanism. Thus, ECP combines both membrane destabilization and enzymatic activities to effect parasite killing. Taken together, our data highlight the microbicidal versatility of ECP as an innate immunity component and support the development of cell-penetrating RNases as putative leishmanicidal agents.

Validation of a mixture of rK26 and rK39 antigens from Iranian strain of Leishmania infantum to detect anti-Leishmania antibodies in human and reservoir hosts.

Hosseini Farash, B., Mohebali, M., Kazemi, B., Fata, A., Hajjaran, H., Akhoundi, B., Raoofian, R., Mastroeni, P., Moghaddas, E., Khaledi, A., Salehi Sangani, G.
21-06-2022
Sci Rep
https://doi.org/10.1038/s41598-022-14490-6

Mediterranean type of visceral leishmaniasis (VL) is a zoonotic parasitic infection. Some provinces of Iran are endemic for VL while other parts are considered as sporadic areas. This study aimed to assess a combination of recombinant K26 and rK39 antigens as well as crude antigen (CA), derived from an Iranian strain of L. infantum, compared to direct agglutination test (DAT) for the detection of VL in humans and domestic dogs as animal reservoir hosts of the disease. A combination of rK26 and rK39 antigens and also CA was evaluated using indirect ELISA on serum samples of 171 VL confirmed humans (n=84) and domestic dogs (n=87) as well as 176 healthy humans (n=86) and domestic dogs (n=90). Moreover, 36 serum samples of humans (n=20) and canines (n=16) with other potentially infectious diseases were collected and tested for finding cross- reactivity. The results of ELISA were compared to DAT, currently considered as gold standard for the serodiagnosis of VL. The sensitivity and specificity, positive predictive and negative predictive values were calculated compared to DAT. The positive sera had previously shown a positive DAT titer ≥ 1:800 for humans and ≥ 1:80 for dogs. Analysis was done by MedCalc and SPSS softwares. Using the combination of rK26 and rK39 in ELISA, a sensitivity of 95.2% and a specificity of 93.0% % were found in human sera at a 1:800 (cut-off) titer when DAT-confirmed cases were compared with healthy controls; a sensitivity of 98.9% and specificity of 96.7%% were found at a 1:80 (cut-off) titer compared with DAT. A good degree of agreement was found between the combined rK39 and rK26-ELISA with DAT in human (0.882) and dog serum samples (0.955) by kappa analysis ($p<0.05$). The ELISA using the CA test showed 75% sensitivity in human and 93.1% in dog serum samples as well as 53.5% specificity in human and 83.3% in dog,s sera, respectively. The combination of rK26 and rK39 recombinant antigen prepared from Iranian strain of Leishmania infantum showed high accuracy for the serodiagnosis of VL in human and domestic dogs. Further extended field trial with a larger sample size is recommended.

Cutaneous leishmaniasis in travellers and migrants: a 10-year case series in a Canadian reference centre for tropical diseases.

Lemieux, A., Lagacé, F., Billick, K., Ndao, M., Yansouni, C., Semret, M., Libman, M., Barkati, S.
21-06-2022
CMAJ Open
https://doi.org/10.9778/cmajo.20210238

Cutaneous leishmaniasis is increasingly encountered in returned travellers and migrants to nonendemic countries. We sought to describe the clinical characteristics and treatment outcomes of cases of cutaneous leishmaniasis diagnosed at our reference centre over a 10-year period. This case series included all laboratory-confirmed cases of cutaneous leishmaniasis in travellers and migrants for whom complete clinical data were available, diagnosed between January 2008 and October 2018 at the J.D. MacLean Centre for Tropical Diseases in Montréal. We examined the number of cases each year. We used descriptive statistics to summarize variables (e.g., demographic characteristics, travel history, clinical presentation, diagnostic methods, treatments, adverse events) extracted from the patients' electronic medical records. The primary outcome for evaluating clinical response to treatment was defined as the complete re-epithelialization of the wound surface at 1 year. We identified 48 patients who received diagnoses of cutaneous leishmaniasis in the 10-year

study period, including 33 exposed in the Americas and 15 exposed in other regions (median age 43.5 [range 1-75] yr); 28 [58%] males). The annual number of cases increased from 9 in 2008/09 to 16 in 2017/18. The median time from onset to diagnosis was 89 (IQR 58-134) days. Liposomal amphotericin B was the most commonly used initial treatment (20 [53%] patients). Thirty-five patients completed their follow-up, and 11 had successful response to 1 course of liposomal amphotericin B. Adverse events (including acute kidney injury, increased pancreatic enzymes and fatigue) were reported in 6 (30%) patients. Clinical cure was achieved within 1 year for 32 (91%) of the 35 patients who completed follow-up. This study showed an increase in the number of cases of cutaneous leishmaniasis seen in our centre over the study period, likely because of increased travel and migration. This diagnosis should be considered in travellers and migrants with a chronic cutaneous lesion.

CYSTICERCOSE

DRACUNCULOSE

ECHINOCOCCOSE

Bacterial and Fungal Occurrence in Hydatid Cysts from Livestock in Central Iran.

Zandi, S., Mariconti, M., Zandi, H., Jafari, A., Hajimohammadi, B., Eslami, G., Vakili, M., Sheykhzadegan, M., Askari, V., Hosseini, S.
22-06-2022
Vet Res Commun
https://doi.org/10.1007/s11259-022-09959-8

Echinococcus granulosus sensu lato causes Cystic echinococcosis. This study investigated the bacterial and fungal species in the liver and lung hydatid cysts obtained from sheep, goats, cattle, and camels slaughtered in Yazd abattoir, Central Iran. In this study, 84 hydatid cysts were obtained from 20 sheep, 13 goats, 25 cattle, and 26 camels. The fertility and viability rates were assessed using light microscopy and eosin staining, respectively. The aspirated hydatid cysts were cultured to detect the presence of any bacteria and fungi. Bacterial isolates were identified by biochemical tests. DNA was also extracted from germinal layers, and then genotyping was carried out targeting the cox 1 gene. The statistical analysis was performed by SPSS version 16.0. This study showed that 22.62% (19/84) of hydatid cysts had bacterial occurrence, and none of the samples had fungal species. Among the fertile cysts, 52.6% had bacterial occurrence, of which 40% were viable. Most bacteria detected in hydatid cysts included Staphylococcus saprophyticus, Escherichia coli, and S. epidermidis. Hydatid cysts with bacterial occurrence were identified as G1-G3, G5, and G6/G7. The bacterial species occurrence in hydatid cysts had no significant relationship with fertility and viability (P>0.05), without any significant relation with viability (P>0.05), animal species (P>0.05), involved organ in animals (P>0.05), and hydatid cyst genotypes (P>0.05). It should also be mentioned that this is the first study to assess the relationship between hydatid cyst genotyping and the occurrence of fungal and bacterial species.

TREMATODOSES D'ORIGINE ALIMENTAIRE (CLONORCHIASE, OPISTHORCHIASE, FASCIOLASE ET PARAGONIMOSE)

FILARIOSE LYMPHATIQUE

MYCETOME

Ultrasound-guided Fine Needle Aspiration Cytology significantly improved mycetoma diagnosis.

Siddig, E., El Had Bakhait, O., El Nour Bahar, M., Siddig Ahmed, E., Bakhiet, S., Motasim Ali, M., Babekir Abdallah, O., Ahmed Hassan, R., Verbon, A., van de Sande, W., Fahal, A.
24-06-2022
J Eur Acad Dermatol Venereol
https://doi.org/10.1111/jdv.18363

Ultrasound (US)-guided fine-needle aspiration cytology (US-FNAC) has improved the diagnosis of many malignancies, infections, and other diseases as it is safe, simple, quick and accurate. In mycetoma, it is assumed that this technique may have a better diagnostic yield than the conventional FNAC as it can accurately identify the optimal site for the aspiration. to compare the diagnostic yield of conventional FNAC with US-FNAC. This descriptive cross-sectional hospital-based study included 80 patients with clinically suspected mycetoma. From the 80 patients included, 35 proved to have actinomycetoma, and 37 had eumycetoma based on surgical biopsies, histopathological examination and the culture of grains. Eight patients appeared to have no mycetoma. For actinomycetoma diagnosis, the US-guided FNAC improved sensitivity to 97%

and negative predictive value (NPV) to 83% compared to the conventional FNAC, which had 63% sensitivity; and NPV of 28%. No improvement was found for specificity. For eumycetoma, the conventional FNAC, had 86.5% sensitivity, 100% specificity, 100% PPV and 37.5% NPV. The US-FNAC for the diagnosis of eumycetoma had 100% sensitivity and specificity. The obtained results showed that US-FNAC is better than the conventional FNAC with lower false-negative results. It can accurately distinguish between the two types of mycetoma, allowing rapid initiation of proper treatment. The technique can be used in rural areas with low resources and for epidemiological surveys as a quick screening tool for patients suspected of mycetoma.

ONCHOCERCOSE

SCHISTOSOMIASE

Frequency distribution of cytokine and associated transcription factor single nucleotide polymorphisms in Zimbabweans: Impact on schistosome infection and cytokine levels.

Hanton, A., Scott, F., Stenzel, K., Nausch, N., Zdesenko, G., Mduluza, T., Mutapi, F.
27-06-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010536

Cytokines mediate T-helper (TH) responses that are crucial for determining the course of infection and disease. The expression of cytokines is regulated by transcription factors (TFs). Here we present the frequencies of single nucleotide polymorphisms (SNPs) in cytokine and TF genes in a Zimbabwean population, and further relate SNPs to susceptibility to schistosomiasis and cytokine levels. Individuals (N = 850) were genotyped for SNPs across the cytokines IL4, IL10, IL13, IL33, and IFNG, and their TFs STAT4, STAT5A/B, STAT6, GATA3, FOXP3, and TBX21 to determine allele frequencies. Circulatory levels of systemic and parasite-specific IL-4, IL-5, IL-10, IL-13, and IFNγ were quantified via enzyme-linked immunosorbent assay. Schistosoma haematobium infection was determined by enumerating parasite eggs excreted in urine by microscopy. SNP allele frequencies were related to infection status by case-control analysis and logistic regression, and egg burdens and systemic and parasite-specific cytokine levels by analysis of variance and linear regression. Novel findings were i) IL4 rs2070874*T's association with protection from schistosomiasis, as carriage of ≥1 allele gave an odds ratio of infection of 0.597 (95% CIs, 0.421-0.848, p = 0.0021) and IFNG rs2069727*G's association with susceptibility to schistosomiasis as carriage of ≥1 allele gave an odds ratio of infection of 1.692 (1.229-2.33, p = 0.0013). Neither IL4 rs2070874*T nor IFNG rs2069727*G were significantly associated with cytokine levels. This study found TH2-upregulating SNPs were more frequent among the Zimbabwean sample compared to African and European populations, highlighting the value of immunogenetic studies of African populations in the context of infectious diseases and other conditions, including allergic and atopic disease. In addition, the identification of novel infection-associated alleles in both TH1- and TH2-associated genes highlights the role of both in regulating and controlling responses to Schistosoma.

RIP3 deficiency attenuated hepatic stellate cell activation and liver fibrosis in schistosomiasis through JNK-cJUN/Egr1 downregulation.

Song, L., Yin, X., Guan, S., Gao, H., Dong, P., Mei, C., Yang, Y., Zhang, Y., Yu, C., Hua, Z.
27-06-2022
Signal Transduct Target Ther
https://doi.org/10.1038/s41392-022-01019-6

A new accumulation assay of Schistosoma mansoni miracidia using square capillary glass tubes.

Miura, M., Mitsui, Y., Aoki, Y., Kato, K.
23-06-2022
Exp Parasitol
https://pubmed.ncbi.nlm.nih.gov/35753412

Current control measures for schistosomiasis have only been partially successful in endemic areas due to socioeconomic constraints. One possibility for controlling the disease is to aim at the miracidial stage of the trematode to avoid infecting intermediate snail hosts by introducing more attractive substances for miracidia in the environment. Here, we introduce an accumulation assay of Schistosoma mansoni miracidia using a square glass tube for analysis of the positive responses of miracidia toward several substances, including snail-conditioned water of Biomphalaria glabrata, Bulinus globosus and insusceptible snails collected in the Nagasaki area in Japan. The substances are not proteins because miracidia accumulated in boiled snail-conditioned water and the secretion or emission level of substances depended on the feeding conditions of Biomphalaria glabrata. The present study also showed that substances emitted from Biomphalaria glabrata with a molecular weight around 10 kDa accumulated Schistosoma mansoni miracidia. Further, we showed that Schistosoma mansoni miracidia did not accumulate in response to mono- or disaccharides tested in the study.

[Consensus document for the management of schistosomiasis in Primary Care].

Salas-Coronas, J., Pérez Pérez, A., Roure, S., Sánchez Peinador, C., Santos Larrégola, L., Arranz Izquierdo, J., Bocanegra, C., García López Hortelano, M., García Vázquez, E., Moza Moriñigo, H., Azkune Galparsoro, H.
23-06-2022

Aten Primaria
https://pubmed.ncbi.nlm.nih.gov/35753207

Human schistosomiasis is the parasitic disease with the highest morbidity and mortality worldwide after malaria. It is endemic in more than 78 tropical and subtropical countries, especially in sub-Saharan Africa, and it is estimated that 236 million people are infected. It can cause serious health complications at the genitourinary and hepatosplenic level, leading to the death of 300,000 people each year. The number of imported cases in Western countries has increased in recent years due to the arrival of a significant number of migrants from endemic regions and a growing number of travelers who have visited them. On the other hand, outbreaks of autochthonous transmission have recently been reported in Corsica (France) and Almería (Spain). For all these reasons, the European health authorities have recommended serological screening for the disease in all migrants from endemic areas who have been living in Europe for less than 5 years. Since Primary Care is usually the first point of contact for these people with the Health System, doctors must know the main aspects of the disease, and be provided with the necessary means for its diagnosis and treatment. This document has been prepared by professionals belonging to five scientific societies of Primary Care (SEMFyC, SEMG, SEMERGEN), Pediatrics (SEIP) and Tropical Medicine and International Health (SEMTSI), in order to establish clear recommendations for the diagnosis and management of schistosomiasis in Primary Care.

Burden and factors associated with schistosomiasis and soil-transmitted helminth infections among school-age children in Huambo, Uige and Zaire provinces, Angola.

Bartlett, A., Sousa-Figueiredo, J., van Goor, R., Monaghan, P., Lancaster, W., Mugizi, R., Mendes, E., Nery, S., Lopes, S.
25-06-2022
Infect Dis Poverty
https://doi.org/10.1186/s40249-022-00975-z

Schistosomiasis and soil-transmitted helminths (STHs) contribute high disease burdens amongst the neglected tropical diseases (NTDs) and are public health problems in Angola. This study reports the prevalence, intensity and risk factors for schistosomiasis and STH infection in Huambo, Uige and Zaire provinces, Angola, to inform a school-based preventive chemotherapy program. A two-stage cluster design was used to select schools and schoolchildren to participate in parasitological and water, sanitation and hygiene (WASH) surveys across Huambo, Uige, and Zaire provinces. Point-of-care circulating cathodic antigen and urinalysis rapid diagnostic tests (RDTs) were used to determine the prevalence of Schistosoma mansoni and S. haematobium, respectively. Kato-Katz was used to identify and quantify STH species and quantify and compare with RDTs for S. mansoni. Urine filtration was used to quantify and compare with RDTs for S. haematobium. Descriptive statistics were used for prevalence and infection intensity of schistosomiasis and STH infection. Performance of RDTs was assessed through specificity and Cohen's Kappa agreement with microscopy. A multivariate regression analysis was used to determine demographic and WASH factors associated with schistosomiasis and STH infection. A total 575 schools and 17,093 schoolchildren participated in the schistosomiasis survey, of which 121 schools and 3649 schoolchildren participated in the STH survey. Overall prevalence of S. mansoni was 21.2% (municipality range 0.9-74.8%) and S. haematobium 13.6% (range 0-31.2%), with an overall prevalence of schistosomiasis of 31.4% (range 5.9-77.3%). Overall prevalence of Ascaris lumbricoides was 25.1% (range 0-89.7%), hookworm 5.2% (range 0-42.6%), and Trichuris trichiura 3.6% (range 0-24.2%), with an overall prevalence of STH infection of 29.5% (range 0.8-89.7%). Ecological zone and ethnicity were factors associated with schistosomiasis and STH infection, with older age and female sex additional risk factors for S. haematobium. Most municipalities met World Health Organization defined prevalence thresholds for a schistosomiasis preventive chemotherapy program. A STH preventive chemotherapy program is indicated for nearly all municipalities in Uige and select municipalities in Huambo and Zaire. The association between ecological zone and ethnicity with schistosomiasis and STH infection necessitates further evaluation of home and school environmental, sociodemographic and behavioural factors to inform targeted control strategies to complement preventive chemotherapy programs.

Sarcopenia, body composition and factors associated with variceal gastrointestinal bleeding and splenectomy in hepatosplenic schistosomiasis mansoni.

Barbosa, F., Nardelli, M., Cançado, G., Silva, C., Osório, F., Melo, R., Taranto, D., Ferrari, T., Couto, C., Faria, L.
24-06-2022
Trans R Soc Trop Med Hyg
https://pubmed.ncbi.nlm.nih.gov/35748511

Sarcopenia is a common complication of cirrhosis and an important predictor of morbimortality. We aimed to determine the prevalence of sarcopenia and its associated factors in hepatosplenic schistosomiasis (HSS) as well as to evaluate whether muscle mass and function are associated with variceal upper gastrointestinal bleeding (VUGIB) and previous splenectomy in subjects without other liver diseases. We conducted a cross-sectional study including adults with HSS who underwent clinical, biochemical, anthropometric, muscle strength and physical performance evaluations and were submitted to bioelectrical impedance analysis and abdominal ultrasound. Sarcopenia was diagnosed according to the 2019 European consensus criteria. A total of 66 patients with HSS (62.1% male; mean age 48.8±8.6 y) were included. Overall, six subjects (9.1%) were diagnosed with probable sarcopenia and none had confirmed sarcopenia. Fat-free body mass index (BMI) was independently associated with VUGIB (odds ratio 0.701 [95% confidence interval 0.51 to 0.96]; p=0.025). Compared with patients who did not undergo

surgery, individuals who underwent esophagogastric devascularization combined with splenectomy (EGDS) had higher serum lipid levels, fat percentage and frequency of metabolic syndrome, with lower skeletal muscle mass index and hand grip strength. HSS mansoni seems not to cause sarcopenia. However, a lower fat-free BMI was associated with previous VUGIB and the subgroup of patients who underwent EGDS presented higher lipid levels, fat percentage and frequency of metabolic syndrome and lower muscle mass and function.

A simple and efficient miracidium hatching technique for preparing a single-genome DNA sample of Schistosoma japonicum.

Wanlop, A., Dang-Trinh, M., Kirinoki, M., Suguta, S., Shinozaki, K., Kawazu, S.
22-06-2022
J Vet Med Sci
https://doi.org/10.1292/jvms.21-0536

In this study, a simple and efficient miracidium hatching technique (MHT) protocol for preparing a single-genome DNA of Schistosoma japonicum was proposed. The protocol was designed with 96-well plates to collect a miracidium for single-genome DNA preparation, and the effects of lighting conditions on hatching rates were evaluated. The highest hatching rate was recorded under sunlight (92.4%), followed by fluorescent light (88.0%), and the lowest rate was recorded under the dark condition (4.7%). The results suggested for the first time, to our knowledge, that sunlight was efficient for this simple MHT protocol. Successful amplification of microsatellite marker genes using DNA isolated from a single miracidium also confirmed the quality of the single-genome DNA for subsequent applications.

Effects of Structurally Different HDAC Inhibitors against *Trypanosoma cruzi*, *Leishmania*, and *Schistosoma mansoni*.

Di Bello, E., Noce, B., Fioravanti, R., Zwergel, C., Valente, S., Rotili, D., Fianco, G., Trisciuoglio, D., Mourão, M., Sales, P., Lamotte, S., Prina, E., Späth, G., Häberli, C., Keiser, J., Mai, A.
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Neglected tropical diseases (NTDs), including trypanosomiasis, leishmaniasis, and schistosomiasis, result in a significant burden in terms of morbidity and mortality worldwide every year. Current antiparasitic drugs suffer from several limitations such as toxicity, no efficacy toward all of the forms of the parasites' life cycle, and/or induction of resistance. Histone-modifying enzymes play a crucial role in parasite growth and survival; thus, the use of epigenetic drugs has been suggested as a strategy for the treatment of NTDs. We tested structurally different HDACi **1**-**9**, chosen from our in-house library or newly synthesized, against *Trypanosoma cruzi, Leishmania* spp, and *Schistosoma mansoni*. Among them, **4** emerged as the most potent against all of the tested parasites, but it was too toxic against host cells, hampering further studies. The retinoic 2'-aminoanilide **8** was less potent than **4** in all parasitic assays, but as its toxicity is considerably lower, it could be the starting structure for further development. In *T. cruzi*, compound **3** exhibited a single-digit micromolar inhibition of parasite growth combined with moderate toxicity. In *S. mansoni*, **4**'s close analogs **17**-**20** were tested in new transformed schistosomula (NTS) and adult worms displaying high death induction against both parasite forms. Among them, **17** and **19** exhibited very low toxicity in human retinal pigment epithelial (RPE) cells, thus being promising compounds for further optimization.

Evaluation of antibody serology to determine current helminth and Plasmodium falciparum infections in a co-endemic area in Southern Mozambique.

Santano, R., Rubio, R., Grau-Pujol, B., Escola, V., Muchisse, O., Cuamba, I., Vidal, M., Ruiz-Olalla, G., Aguilar, R., Gandasegui, J., Demontis, M., Jamine, J., Cossa, A., Sacoor, C., Cano, J., Izquierdo, L., Chitnis, C., Coppel, R., Chauhan, V., Cavanagh, D., Dutta, S., Angov, E., van Lieshout, L., Zhan, B., Muñoz, J., Dobaño, C., Moncunill, G.
21-06-2022
PLoS Negl Trop Dis
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Soil-transmitted helminths (STH), Schistosoma spp. and Plasmodium falciparum are parasites of major public health importance and co-endemic in many sub-Saharan African countries. Management of these infections requires detection and treatment of infected people and evaluation of large-scale measures implemented. Diagnostic tools are available but their low sensitivity, especially for low intensity helminth infections, leaves room for improvement. Antibody serology could be a useful approach thanks to its potential to detect both current infection and past exposure. We evaluated total IgE responses and specific-IgG levels to 9 antigens from STH, 2 from Schistosoma spp., and 16 from P. falciparum, as potential markers of current infection in a population of children and adults from Southern Mozambique (N = 715). Antibody responses were measured by quantitative suspension array Luminex technology and their performance was evaluated by ROC curve analysis using microscopic and molecular detection of infections as reference. IgG against the combination of EXP1, AMA1 and MSP2 (P. falciparum) in children and NIE (Strongyloides stercoralis) in adults and children had the highest accuracies (AUC = 0.942 and AUC = 0.872, respectively) as markers of current infection. IgG against the combination of MEA and Sm25 (Schistosoma spp.) were also reliable markers of current infection (AUC = 0.779). In addition, IgG seropositivity against 20 out of the 27 antigens in the panel differentiated the seropositive endemic population from the non-endemic population, suggesting a possible role as markers of exposure although sensitivity could not be assessed. We provided evidence for the utility of antibody serology to detect current infection with parasites causing

tropical diseases in endemic populations. In addition, most of the markers have potential good specificity as markers of exposure. We also showed the feasibility of measuring antibody serology with a platform that allows the integration of control and elimination programs for different pathogens.

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

Burden and factors associated with schistosomiasis and soil-transmitted helminth infections among school-age children in Huambo, Uige and Zaire provinces, Angola.

Bartlett, A., Sousa-Figueiredo, J., van Goor, R., Monaghan, P., Lancaster, W., Mugizi, R., Mendes, E., Nery, S., Lopes, S.
25-06-2022
Infect Dis Poverty
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Schistosomiasis and soil-transmitted helminths (STHs) contribute high disease burdens amongst the neglected tropical diseases (NTDs) and are public health problems in Angola. This study reports the prevalence, intensity and risk factors for schistosomiasis and STH infection in Huambo, Uige and Zaire provinces, Angola, to inform a school-based preventive chemotherapy program. A two-stage cluster design was used to select schools and schoolchildren to participate in parasitological and water, sanitation and hygiene (WASH) surveys across Huambo, Uige, and Zaire provinces. Point-of-care circulating cathodic antigen and urinalysis rapid diagnostic tests (RDTs) were used to determine the prevalence of Schistosoma mansoni and S. haematobium, respectively. Kato-Katz was used to identify and quantify STH species and quantify and compare with RDTs for S. mansoni. Urine filtration was used to quantify and compare with RDTs for S. haematobium. Descriptive statistics were used for prevalence and infection intensity of schistosomiasis and STH infection. Performance of RDTs was assessed through specificity and Cohen's Kappa agreement with microscopy. A multivariate regression analysis was used to determine demographic and WASH factors associated with schistosomiasis and STH infection. A total 575 schools and 17,093 schoolchildren participated in the schistosomiasis survey, of which 121 schools and 3649 schoolchildren participated in the STH survey. Overall prevalence of S. mansoni was 21.2% (municipality range 0.9-74.8%) and S. haematobium 13.6% (range 0-31.2%), with an overall prevalence of schistosomiasis of 31.4% (range 5.9-77.3%). Overall prevalence of Ascaris lumbricoides was 25.1% (range 0-89.7%), hookworm 5.2% (range 0-42.6%), and Trichuris trichiura 3.6% (range 0-24.2%), with an overall prevalence of STH infection of 29.5% (range 0.8-89.7%). Ecological zone and ethnicity were factors associated with schistosomiasis and STH infection, with older age and female sex additional risk factors for S. haematobium. Most municipalities met World Health Organization defined prevalence thresholds for a schistosomiasis preventive chemotherapy program. A STH preventive chemotherapy program is indicated for nearly all municipalities in Uige and select municipalities in Huambo and Zaire. The association between ecological zone and ethnicity with schistosomiasis and STH infection necessitates further evaluation of home and school environmental, sociodemographic and behavioural factors to inform targeted control strategies to complement preventive chemotherapy programs.

Clinical Presentation and Intensity of Infection with Intestinal Helminths among School Children in Ile-Ife, Osun State, Nigeria.

Olopade, B., Charles-Eromosele, T., Olopade, O.
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West Afr J Med
https://pubmed.ncbi.nlm.nih.gov/35749378

Intestinal helminthiases are public health problems of children in developing countries of the world and account for significant morbidity as it results in stunted growth, intestinal obstruction, anaemia, cognitive impairment, acute pancreatitis, acute cholecystitis and rectal prolapse. This study assessed intestinal helminths, infection intensity and symptoms in primary school children in Ile-Ife. It was a cross sectional study. Three hundred and eighty-four pupils randomly selected from six public primary schools in Ife Central Local Government were enrolled for the study. Ethical approval was obtained. Stool samples were collected and processed using the Formol-ether concentration method. Questionnaires were administered to obtain relevant information. Data entry and processing were done using Microsoft excel and IBM SPSS Statistics for windows, version 17. Statistical analysis included frequency, proportion and percentages. Helminthic parasites were recovered from the stool of the schoolchildren and the overall prevalence of helminthic infection was 24%. Ascaris lumbricoides was the most prevalent (22.1%) with moderate and light intensities of infection, Hookworm (3.4%) with light intensity infection and Hymenolepis nana 0.3%. Symptoms were present in 48.2% of the participants and 31.5% presented with abdominal pain, nausea 22.1%, diarrhoea 21.1%, anorexia 7%. Weight loss, nausea and vomiting were found to be significantly associated with infection with intestinal helminths. Light to moderate intestinal helminthic infections are still prevalent among school children with weight loss, nausea and vomiting being the most significant symptoms. Continuous studies among school children are needed including those in private schools to better understand the epidemiology of these infections.

Higher helminth ova counts and incomplete decomposition in sand-enveloped latrine pits in a coastal sub-district of Bangladesh.

Rahman, M., Islam, M., Doza, S., Naser, A., Shoab, A., Rosenbaum, J., Islam, M., Unicomb, L., Clasen, T., Ercumen, A.
23-06-2022
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Pit latrines are the most common latrine technology in rural Bangladesh, and untreated effluent from pits can directly contaminate surrounding aquifers. Sand barriers installed around the latrine pit can help reduce contamination but can also alter the decomposition of the fecal sludge and accelerate pit fill-up, which can counteract their benefits. We aimed to evaluate whether there was a difference in decomposition of fecal sludge and survival of soil-transmitted helminth (STH) ova among latrines where a 50-cm sand barrier was installed surrounding and at the bottom of the pit, compared to latrines without a sand barrier, in coastal Bangladesh. We assessed decomposition in latrine pits by measuring the carbon-nitrogen (C/N) ratio of fecal sludge. We enumerated Ascaris lumbricoides and Trichuris trichiura ova in the pit following 18 and 24 months of latrine use. We compared these outcomes between latrines with and without sand barriers using generalized linear models with robust standard errors to adjust for clustering at the village level. The C/N ratio in latrines with and without a sand barrier was 13.47 vs. 22.64 (mean difference: 9.16, 95% CI: 0.15, 18.18). Pits with sand barriers filled more quickly and were reportedly emptied three times more frequently than pits without; 27/34 latrines with sand barriers vs. 9/34 latrines without barriers were emptied in the previous six months. Most reported disposal methods were unsafe. Compared to latrines without sand barriers, latrines with sand barriers had significantly higher log10 mean counts of non-larvated A. lumbricoides ova (log10 mean difference: 0.35, 95% CI: 0.12, 0.58) and T. trichiura ova (log10 mean difference: 0.47, 95% CI: 0.20, 0.73). Larvated ova counts were similar for the two types of latrines for both A. lumbricoides and T. trichiura. Our findings suggest that sand barriers help contain helminth ova within the pits but pits with barriers fill up more quickly, leading to more frequent emptying of insufficiently decomposed fecal sludge. Further research is required on latrine technologies that can both isolate pathogens from the environment and achieve rapid decomposition.

Interventions to improve water, sanitation, and hygiene for preventing soil-transmitted helminth infection.

Revue de littérature

Garn, J., Wilkers, J., Meehan, A., Pfadenhauer, L., Burns, J., Imtiaz, R., Freeman, M.
21-06-2022
Cochrane Database Syst Rev
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It is estimated that 1.5 billion people are infected with soil-transmitted helminths (STHs) worldwide. Re-infection occurs rapidly following deworming, and interruption of transmission is unlikely without complementary control efforts such as improvements in water, sanitation, and hygiene (WASH) access and behaviours. To assess the effectiveness of WASH interventions to prevent STH infection. We used standard, extensive Cochrane search methods. The latest search date was 19 October 2021. We included interventions to improve WASH access or practices in communities where STHs are endemic. We included randomized controlled trials (RCTs), as well as trials with an external control group where participants (or clusters) were allocated to different interventions using a non-random method (non-RCTs). We did not include observational study designs. Our primary outcome was prevalence of any STH infection. Prevalence of individual worms was a secondary outcome, including for Ascaris lumbricoides, Trichuris trichiura, hookworm (Ancylostoma duodenale or Necator americanus), or Strongyloides stercoralis. Intensity of infection, measured as a count of eggs per gram of faeces for each species, was another secondary outcome. Two review authors independently reviewed titles and abstracts and full-text records for eligibility, performed data extraction, and assessed risk of bias using the Cochrane risk of bias assessment tool for RCTs and the EPOC tool for non-RCTs. We used a random-effects meta-analysis to pool study estimates. We used Moran's I^2 statistic to assess heterogeneity and conducted subgroup analyses to explore sources of heterogeneity. We assessed the certainty of the evidence using the GRADE approach. We included 32 studies (16 RCTs and 16 non-RCTs) involving a total of 52,944 participants in the review. Twenty-two studies (14 RCTs (16 estimates) and eight non-RCTs (11 estimates)) reported on our primary outcome, prevalence of infection with at least one STH species. Twenty-one studies reported on the prevalence of A lumbricoides (12 RCTs and 9 non-RCTs); 17 on the prevalence of T trichiura (9 RCTs and 8 non-RCTs); 18 on the prevalence of hookworm (10 RCTs and 8 non-RCTs); and one on the prevalence of S stercoralis (1 non-RCT). Sixteen studies measured the intensity of infection for an individual STH type. Ten RCTs and five non-RCTs reported on the intensity of infection of A lumbricoides; eight RCTs and five non-RCTs measured the intensity of infection of T trichiura; and eight RCTs and five non-RCTs measured the intensity of hookworm infection. No studies reported on the intensity of infection of S stercoralis. The overall pooled effect estimates showed that the WASH interventions under study may result in a slight reduction of any STH infection, with an odds ratio (OR) of 0.86 amongst RCTs (95% confidence interval (CI) 0.74 to 1.01; moderate-certainty evidence) and an OR of 0.71 amongst non-RCTs (95% CI 0.54 to 0.94; low-certainty evidence). All six of the meta-analyses assessing individual worm infection amongst both RCTs and non-RCTs had pooled estimates in the preventive direction, although all CIs encapsulated the null, leaving the possibility of the null or even harmful effects; the certainty of the evidence ranged from very low to moderate. Individual studies assessing intensity of infection showed mixed evidence supporting WASH. Subgroup analyses focusing on narrow specific subsets of water, sanitation, and hygiene interventions did very little to elucidate which interventions might be better than others. Data on intensity of infection (e.g. faecal egg count) were reported in a variety of ways

across studies, precluding the pooling of results for this outcome. We did not find any studies reporting adverse events resulting from the WASH interventions under study or from mass drug administration (MDA). Whilst the available evidence suggests that the WASH interventions under study may slightly protect against STH infection, WASH also serves as a broad preventive measure for many other diseases that have a faecal oral transmission route of transmission. As many of the studies were done in addition to MDA/deworming (i.e. MDA was ongoing in both the intervention and control arm), our data support WHO recommendations for implementation of improvements to basic sanitation and adequate access to safe water alongside MDA. The biological plausibility for improved access to WASH to interrupt transmission of STHs is clear, but WASH interventions as currently delivered have shown impacts that were lower than expected. There is a need for more rigorous and targeted implementation research and process evaluations in order that future WASH interventions can better provide benefit to users. Inconsistent reporting of the intensity of infection underscores the need to define the minimal, standard data that should be collected globally on STHs to enable pooled analyses and comparisons.

Evaluation of antibody serology to determine current helminth and Plasmodium falciparum infections in a co-endemic area in Southern Mozambique.

Santano, R., Rubio, R., Grau-Pujol, B., Escola, V., Muchisse, O., Cuamba, I., Vidal, M., Ruiz-Olalla, G., Aguilar, R., Gandasegui, J., Demontis, M., Jamine, J., Cossa, A., Sacoor, C., Cano, J., Izquierdo, L., Chitnis, C., Coppel, R., Chauhan, V., Cavanagh, D., Dutta, S., Angov, E., van Lieshout, L., Zhan, B., Muñoz, J., Dobaño, C., Moncunill, G.
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Soil-transmitted helminths (STH), Schistosoma spp. and Plasmodium falciparum are parasites of major public health importance and co-endemic in many sub-Saharan African countries. Management of these infections requires detection and treatment of infected people and evaluation of large-scale measures implemented. Diagnostic tools are available but their low sensitivity, especially for low intensity helminth infections, leaves room for improvement. Antibody serology could be a useful approach thanks to its potential to detect both current infection and past exposure. We evaluated total IgE responses and specific-IgG levels to 9 antigens from STH, 2 from Schistosoma spp., and 16 from P. falciparum, as potential markers of current infection in a population of children and adults from Southern Mozambique (N = 715). Antibody responses were measured by quantitative suspension array Luminex technology and their performance was evaluated by ROC curve analysis using microscopic and molecular detection of infections as reference. IgG against the combination of EXP1, AMA1 and MSP2 (P. falciparum) in children and NIE (Strongyloides stercoralis) in adults and children had the highest accuracies (AUC = 0.942 and AUC = 0.872, respectively) as markers of current infection. IgG against the combination of MEA and Sm25 (Schistosoma spp.) were also reliable markers of current infection (AUC = 0.779). In addition, IgG seropositivity against 20 out of the 27 antigens in the panel differentiated the seropositive endemic population from the non-endemic population, suggesting a possible role as markers of exposure although sensitivity could not be assessed. We provided evidence for the utility of antibody serology to detect current infection with parasites causing tropical diseases in endemic populations. In addition, most of the markers have potential good specificity as markers of exposure. We also showed the feasibility of measuring antibody serology with a platform that allows the integration of control and elimination programs for different pathogens.

GALE

Increasing incidence of reported scabies infestations in the Netherlands, 2011-2021.

van Deursen, B., Hooiveld, M., Marks, S., Snijdewind, I., van den Kerkhof, H., Wintermans, B., Bom, B., Schimmer, B., Fanoy, E.
24-06-2022
PLoS One
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Several Public Health Services and general practitioners in the Netherlands observed an increase in scabies in the Netherlands. Since individual cases of scabies are not notifiable in the Netherlands, the epidemiological situation is mostly unknown. To investigate the scabies incidence in the Netherlands, we described the epidemiology of scabies between 2011 and 2021. Two national data sources were analysed descriptively. One data source obtained incidence data of scabies (per 1,000 persons) of persons consulting in primary care from 2011-2020. The other data source captured the number of prescribed scabicides in the Netherlands from 2011-2021. To describe the correlation between the incidence of diagnoses and the number of dispensations between 2011 and 2020, we calculated a correlation coefficient. The incidence of reported scabies has increased by more than threefold the last decade (2011-2020), mainly affecting adolescents and (young) adults. This was also clearly reflected in the fivefold increase in dispensations of scabicide medication during 2011-2021. The incidence and dispensations were at an all-time high in 2021. We found a strong correlation between the reported incidence and the number of dispensations between 2011 and 2020. More awareness on early diagnosis, proper treatment and treatment of close contacts is needed.

Scabies epidemiology in health care centers for refugees and asylum seekers in Greece.

Louka, C., Logothetis, E., Engelman, D., Samiotaki-Logotheti, E., Pournaras, S., Stienstra, Y.

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Scabies is a global health concern disproportionately affecting vulnerable populations such as refugees and asylum seekers. Greece is a main point of entry in Europe for refugees, but epidemiological data on scabies in this population are scarce. We aimed to describe the epidemiology of scabies, including trends over the study period. Data were collected from June, 2016 to July, 2020, using the surveillance system of the Greek National Public Health Organization. Daily reports on scabies and other infectious diseases were submitted by staff at health centers for refugees/asylum seekers. Observed proportional morbidity for scabies was calculated using consultations for scabies as a proportion of total consultations. There were a total of 13118 scabies cases over the study period. Scabies was the third most frequently observed infectious disease in refugees/asylum seekers population after respiratory infections and gastroenteritis without blood in the stool. The scabies monthly observed proportional morbidity varied between 0.3% (August 2017) to 5.7% (January 2020). Several outbreaks were documented during the study period. The number of cases increased from October 2019 until the end of the study period, with a peak of 1663 cases in January 2020, related to an outbreak at one center. Spearman correlation test between the number of reported scabies cases and time confirmed an increasing trend (ρ = 0.67). Scabies is one of the most frequently reported infectious diseases by health care workers in refugee/asylum seekers centers in Greece. Observed proportional morbidity for scabies increased over time and there were several outbreaks. The current surveillance system with daily reports of the new cases effectively detects new cases in an early stage. Public health interventions, including mass drug administration, should be considered to reduce the burden of scabies in refugee/migrant populations.

MORSURES DE SERPENT

Production of a murine mAb against Bothrops alternatus and B. neuwiedi snake venoms and its use to isolate a thrombin-like serine protease fraction.

Belo, A., Naves de Souza, D., de Melo-Braga, M., de Souza, L., Molina Molina, D., Vaz de Melo, P., Larsen, M., Guerra-Duarte, C., Chávez-Olórtegui, C.
23-06-2022
Int J Biol Macromol
https://pubmed.ncbi.nlm.nih.gov/35753516

Accidents with snakes from the genus Bothrops represent ~90 % of all snakebites in Brazil. Monoclonal antibodies (mAbs) targeting venom components can be important assets for treating envenoming syndromes, for developing diagnostic tests and for research purposes. Therefore, in this study, we aimed to generate murine mAbs against the antigenic mixture of Bothropic venoms traditionally used as immunogen to produce Bothropic antivenoms in Brazil. ELISA showed that one of the produced mAbs recognizes B. alternatus and B. neuwiedi venoms (mAb anti-Ba/Bn) specifically and Western Blot revealed that this mAb binds to a single protein band of molecular mass of ≈50 kDa. MAb anti-Ba/Bn inhibited the coagulant activity but was unable to neutralize hemorrhagic and phospholipase A2 activities caused by the B. neuwiedi venom. MAb anti-Ba/Bn was immobilized to Sepharose beads and used for immunoaffinity chromatography of B. neuwiedi venom. Proteolytic activity assays indicated that the immunoaffinity-purified fraction (BnF-Bothrops neuwiedi fraction) has a serine protease thrombin-like profile, which was supported by coagulability assays in mice. Bottom-up proteomic analysis confirmed the prevalence of serine proteases in BnF using label-free quantification. In conclusion, this work characterized a mAb with neutralizing properties against B. neuwiedi coagulant activity and demonstrates that immunoaffinity chromatography using mAbs can be a useful technique for purification of bioactive toxic proteins from Bothrops spp. snake venoms.

Bothrops lanceolatus snake venom impairs mitochondrial respiration and induces DNA release in human heart preparation.

Cano-Sanchez, M., Ben-Hassen, K., Louis, O., Dantin, F., Gueye, P., Roques, F., Mehdaoui, H., Resiere, D., Neviere, R.
21-06-2022
PLoS Negl Trop Dis
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Envenomations by Bothrops snakebites can induce overwhelming systemic inflammation ultimately leading to multiple organ system failure and death. Release of damage-associated molecular pattern molecules (DAMPs), in particular of mitochondrial origin, has been implicated in the pathophysiology of the deregulated innate immune response. To test whether whole Bothrops lanceolatus venom would induce mitochondrial dysfunction and DAMPs release in human heart preparations. Human atrial trabeculae were obtained during cannulation for cardiopulmonary bypass from patients who were undergoing routine coronary artery bypass surgery. Cardiac fibers were incubated with vehicle and whole Bothrops lanceolatus venom for 24hr before high-resolution respirometry, mitochondrial membrane permeability evaluation and quantification of mitochondrial DNA. Compared with vehicle, incubation of human cardiac muscle with whole Bothrops lanceolatus venom for 24hr impaired respiratory control ratio and mitochondrial membrane permeability. Levels of mitochondrial DNA increased in the medium of cardiac cell preparation incubated with venom of Bothrops lanceolatus. Our study suggests that whole venom of Bothrops lanceolatus impairs mitochondrial oxidative phosphorylation capacity and increases mitochondrial membrane permeability. Cardiac mitochondrial dysfunction associated with mitochondrial DAMPs release may alter

myocardium function and engage the innate immune response, which may both participate to the cardiotoxicity occurring in patients with severe envenomation.